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(54) Phantom having similar optical characteristics to living tissues.

(57) A phantom having similar light scattering characteristics to living tissues of interest is obtained by suspending in a selected medium (2) a mixture of particles (3) of different-valued radius r_k at respective values of concentration C_k which are determined on the basis of the following matrix equation:

$$\begin{bmatrix} P_{meas}(\theta_1) \\ \vdots \\ P_{meas}(\theta_i) \\ \vdots \\ P_{meas}(\theta_n) \end{bmatrix} = \begin{bmatrix} P(\theta_1,r_1) & \cdots & P(\theta_1,r_m) \\ \vdots & \ddots & \vdots \\ P(\theta_i,r_k) & & \\ \vdots & & \\ P(\theta_n,r_1) & \cdots & P(\theta_n,r_m) \end{bmatrix} \begin{bmatrix} C_1 \\ \vdots \\ C_k \\ \vdots \\ C_m \end{bmatrix}$$

where $P_{meas}(\theta_i)$ is a scattering intensity of light with the living tissues at a scattering angle θ_i and $P(\theta_i,r_k)$ is a scattering intensity with the particles having the radius r_k at the scattering angle θ_i.

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PHANTOM HAVING SIMILAR OPTICAL CHARACTERISTICS TO LIVING TISSUES

The present invention relates to a phantom having optical characteristics, in particular light-scattering characteristics, that are similar to those of living tissues.

Cerebral hemorrhage and inadequate supply of oxygen to brain cells have been either the primary cause of the death of newborn babies in an ICU (Intensive Care Unit) or one of the causes that make them handicapped throughout their life. Bleeding in the brain can be readily discovered by ultrasonic diagnosis or by other imaging techniques. However, hypoxia of brain cells, as with cysts in porencephalic patients and other deficiencies of brain tissues, cannot be detected until after about 3 weeks have passed since the occurrence of the damage. Hypoxia in the brain cells of newborn babies has even become a social concern for medical institutions in developed countries. In Great Britain, intranatal deaths resulting from asphyxia account for one third of the causes of natal death. In other words, three out of 1,000 newborn babies die of suffocation and at least an equal number of babies who survive will be handicapped on account of asphyxia.

Under these medical and social circumstances, a need has arisen for the development of a diagnostic apparatus that allows direct measurement of oxygen supply to brain cells. Tissues and bones of human bodies exhibit a fairly good transparency to light in the near infrared region. Furthermore, in this wavelength range, hemoglobin and cytochrome which are vectors of oxygen transport through the body undergo a change in their absorption spectra depending upon whether they are oxidized or reduced. Therefore, the change in the amount of oxygen supply to the brain can be detected by irradiating the head with near infrared light in the wavelength range of 700 - 900 nm and measuring the change in the spectrum of light that has been transmitted through the head.

Various diagnostic devices have so far been proposed on the basis of the principle described above and their operation consists essentially of guiding light from a near infrared laser diode to the head via fiber optics and detecting the transmitted light from the head (see, for example, U.S. Patent Nos. 4,223,680 and 4,281,645). These devices are adapted to measure the overall (average) change in the quantity of oxygen in the brain. Techniques for determining the distribution of oxygen in the brain have also been investigated and some of them are discussed in "Bioinstrumentation Using Light -- Roads to Optical CT" in O plus E, May 1987 to April 1988.

One of the prerequisites for the development of devices of the type described above is the use of a phantom, or a volume of material that has optical characteristics (absorption and scattering) equivalent to those of brain tissues, and this phantom is required to be stable and to ensure reproducible results.

An oil-in-water emulsion has been conventionally used as a phantom but this is not highly stable and suffers the disadvantage of experiencing a change in particle size with time. A further problem is that the particles in the emulsion often become too small to realize optical characteristics similar to those of living tissues of interest.

According to the present invention, a phantom has similar optical characteristics to living tissues with respect to light-scattering characteristics such as the scattering distribution and has a structure that in a selected medium is suspended a mixture of particles of different-valued radius r_k (k is a positive integer of 1 to m) at respective values of concentration C_k which are determined on the basis of the following matrix equation:

$$\begin{bmatrix} P_{meas}(\theta_1) \\ \vdots \\ P_{meas}(\theta_i) \\ \vdots \\ P_{meas}(\theta_n) \end{bmatrix} = \begin{bmatrix} P(\theta_1, r_1) & \cdots & P(\theta_1, r_m) \\ \vdots & \ddots & \vdots \\ & P(\theta_i, r_k) & \\ \vdots & \ddots & \vdots \\ P(\theta_n, r_1) & \cdots & P(\theta_n, r_m) \end{bmatrix} \begin{bmatrix} C_1 \\ \vdots \\ C_k \\ \vdots \\ C_m \end{bmatrix}$$

where $P_{meas}(\theta_i)$ is a scattering intensity with the living tissues at a scattering angle of θ_i (i is a positive integer of 1 to n) and $P(\theta_i, r_k)$ is a scattering intensity with a particle having the radius r_k).

According to the present invention, a phantom having similar optical characteristics to living tissues of interest can be produced by merely incorporating different-sized particles in a medium. Particularly high stability and reproducibility can be realised by selecting particles whose specific gravity is generally the same as that of the medium (this may be achieved by mixing polystyrene particles with water for example).

Examples of phantoms in accordance with this invention will now be described with reference to the

accompanying drawings in which:-

Fig. 1 shows how to determine a distribution of light scattering on the basis of measured data;

Fig. 2 shows specific procedures of forming a phantom;

Fig. 3 is a graph showing the scattering characteristics of a phantom composed of two kinds of polystyrene particles; and,

Fig. 4 and 5 are diagrams illustrating two typical uses of the phantom of the present invention.

A phantom of the present invention is prepared by suspending different-sized particles in a medium. The particles to be suspended desirably have a specific gravity that is generally the same as that of the medium. This condition may be satisfied by suspending polystyrene particles in water. The wavelength range in which optical characteristics of interest are to be measured is desirably that of near infrared radiation (e.g. 700 - 900 nm) and the absorption of light by polystyrene particles is negligible in this wavelength range.

The phantom of the present invention is formed by suspending a mixture of particles, say, polystyrene particles, of different-valued radius r_k (k is a positive integer of 1 to m) at respective values of concentration C_k in a selected medium, say, water. The respective values of C_k are determined as follows. If the measured scattering distribution with living tissues at a scattering angle of θ_i (i is a positive integer of 1 to n) is written as $P_{meas}(\theta_i)$ and if the calculated or measured scattering distribution with polystyrene particles having the radius r_k is written as $P(\theta_i,r_k)$, then the concentration, C_k, of polystyrene particles having a specific value of radius r_k can be determined on the basis of the following matrix equation:

$$\begin{bmatrix} P_{meas}(\theta_1) \\ \vdots \\ P_{meas}(\theta_i) \\ \vdots \\ P_{meas}(\theta_n) \end{bmatrix} = \begin{bmatrix} P(\theta_1,r_1) & \cdots & P(\theta_1,r_m) \\ \vdots & \ddots & \vdots \\ & P(\theta_i,r_k) & \\ \vdots & & \vdots \\ P(\theta_n,r_1) & \cdots & P(\theta_n,r_m) \end{bmatrix} \begin{bmatrix} C_1 \\ \vdots \\ C_k \\ \vdots \\ C_m \end{bmatrix} \quad \cdots (1)$$

The scattering distribution, $P_{meas}(\theta_i)$, given on the left side of equation (1) can be obtained by measuring the scattering characteristics of the tissues of a living organ such as the brain illuminated with incident light. If a profile as shown in Fig. 1 is obtained, which represents the dependence of the intensity of scattered light on the scattering angle, the intensities of scattered light at scattering angles θ_1, θ_i, and θ_n correspond to $P_{meas}(\theta_1)$, $P_{meas}(\theta_i)$ and $P_{meas}(\theta_n)$, respectively.

The scattering distribution, $P(\theta_i,r_k)$, given in the first term of the right side of equation (1) is that of polystyrene particles having a radius of r_k. In general, $P(\theta,r_k)$ is calculated by known Mie theory of light scattering but it may also be determined by actual measurements. In this latter case, the scattering characteristics of polystyrene particles are measured for each value of the radius r_k and $P(\theta,r_k)$ is determined from the obtained data.

On the basis of these measured and calculated values, operations are performed on the matrix equation (1) to determine the concentration of polystyrene particles, C_k, for each value of the radius r_k. Operations with the matrix equation (1) may be performed by the SVD (single value decomposition) method.

Specific procedures of forming the phantom described above are explained hereinafter with reference to Fig. 2.

First, living tissues of the brain are prepared as a sample and illuminated with near infrared light (783 nm) to investigate the characteristics of light scattering in the sample. The results are as shown graphically in Fig. 2(a), with the scattering angle (θ_i) being plotted in degrees on the horizontal axis and the intensity of scattered light being plotted on a logarithmic scale on the vertical axis. This completes the step of determining experimentally the scattering distribution $P_{meas}(\theta i)$.

In the next step, the scattering distribution $P(\theta_i,r_k)$ is calculated by Mie theory of light scattering. On the basis of both the results of this calculation and the measured values shown in Fig. 2(a), the concentration of polystyrene particles, C_k, is calculated for each value of the radius r_k by equation (1). As for the scattering angle θ_i, this calculation is performed over the range of 0-180° with 1° increments, and as for the radius r_k, calculation is carried out over the range of 0 - 0.6 μm with 0.04 μm increments. The results are as shown graphically in Fig. 2(b), with the horizontal axis plotting the radius of polystyrene particles, r_k, and the vertical axis plotting relative concentration (on a linear scale). One can readily see the presence of two peaks in the graph as denoted by A and B.

The scattering distribution, $P(\theta_i,r_k)$, as determined by Mie theory of light scattering is shown graphically in Fig. 2(c) with the scattering angle plotted on the horizontal axis. The horizontal axis of the graph shown in

Fig. 2(c) corresponds to the scattering angle and has been normalized in accordance with the SVD method.

When polystyrene particles were suspended in water at respective values of the concentration C_k determined for each value of the radius r_k (see Fig. 2(b)), a phantom was obtained that had light-scattering characteristics similar to those of the living tissues. In other words, when the intensity of scattered light was calculated on the basis of the data of concentration C_k shown in Fig. 2(b) for each value of the radius r_k, results as shown in Fig. 2(d) were obtained. One can readily see that the measured data for the actual living tissues which is shown in Fig. 2(a) is in good agreement with the calculated data for the phantom of the present invention which is shown in Fig. 2(d), and the agreement is particularly good at scattering angles in the range of 0 - 90°.

Ideally, the phantom of the present invention is composed of polystyrene particles having many different values of radius. In practice, however, it is difficult and economically infeasible to obtain polystyrene particles having many different values of radius and this necessitates a certain kind of approximation. Thus, noting the two peaks indicated by A and B in Fig. 2(b), one may form a phantom by mixing polystyrene particles having two different radii. Stated more specifically, polystyrene particles having a radius r_1 (= 0.025±0.001 μm) are mixed with polystyrene particles having a radius r_2 (= 0.5±0.015 μm). When these two types of polystyrene particles were suspended in water at respective concentrations of C_1 (= 6.7%) and C2 (= 2.5%), a phantom having the light-scattering characteristics shown in Fig. 3 was obtained. The mean scattering cosine, g, of this phantom was 0.899, which is in very good agreement with the value (g ≃ 0.9) for the actual living tissues.

The mean scattering cosine, g, is a parameter for the directivity of the scattering of particles and is expressed by:

$$g = \int_0^{180°} P(\theta) \cdot \cos\theta \cdot d\theta \qquad \cdots\cdots (2)$$

where θ is the scattering angle and $P(\theta)$ is the scattering intensity. In the case of complete forward scattering (the scattering angle θ is 0° for all particles), g = 1; in the case of complete isotropic scattering, g = 0; and in the case of complete backward scattering (θ = 180° for all particles), g = -1.

A modification of the embodiment described above is explained below. While the distribution of scattering intensity was discussed in the foregoing embodiment, there exists another parameter to described the light scattering, i.e., coefficient of scattering μs. The coefficient of scattering μs is a parameter expressed by the reciprocal of the mean optical pathlength which light travels between successive scatterings, and is given by:

$$\mu_s = \sum_{k=1}^{m} C_k \cdot S_k \qquad \cdots\cdots (3)$$

where r_k is the radius of a particle, C_k is the concentration of particles having the radius r_k, and S_k is the scattering cross section (as determined by Mie theory of light scattering) of the particles of the radius r_k. Therefore, if the relative concentration of particles is determined as shown in Fig. 2(b) by performing operations on the matrix equation (1), the absolute concentration of the particles that yield a predetermined coefficient of scattering μ_s can be determined.

Besides use in evaluating the performance of a certain diagnostic device, the phantom of the present invention has many other applications and three of them are briefly described below.

(1) Determining optical pathlengths in living tissues:

When one wants to measure the change in the quantity of oxygen in the brain, he has to determine the concentrations of hemoglobin, oxidized hemoglobin and other vectors of oxygen transport by measuring the change in light absorption at various wavelengths. In the absence of light scattering, the change in light absorption, ΔA, will be expressed by equation (4) to be given below. When, as shown in Fig. 4, incident light I_o is launched into the brain 1, producing transmitted light I, ΔA is given by:

$$\Delta A = l \cdot \alpha \cdot \Delta C = \Delta \log (I/I_O) \qquad (4)$$

where l is the length of optical path in the brain, α is the absorption coefficient of hemoglobin, and ΔC is

the change in oxygen concentration. Since I and I_o are measurable values and α is known, the change in oxygen concentration ΔC can be determined by equation (4). However, in the presence of light scattering, the effective value of optical pathlength is increased (several times the value shown in Fig. 4), making it impossible to calculate ΔC by equation (4). If, in this case, an experiment is conducted using the phantom of the present invention which has similar optical characteristics to the living tissues, the effective value of ℓ can be determined, thereby allowing ΔC to be calculated by equation (4).

(2) Evaluation of imaging such as oxygen distribution:

In imaging a certain phenomenon such as oxygen distribution in living tissues, experimentation with a phantom and the evaluation of its results are indispensable. For this purpose, three light absorbers are contained in the phantom of the present invention as shown in Fig. 5, where the phantom is indicated by 2 and the light absorbers by 3, and the phantom 2 is illuminated with incident light I_o. By investigating the light transmitted through the phantom, the distribution of the intensity of transmitted light can be obtained in association with the light absorbers, and this allows exact evaluation of a diagnostic device of interest and precise diagnosis experiment, including, e.g., the evaluation of image resolution.

(3) Analysis of light distribution in living tissues:

In performing PDT (photodynamic therapy), it is essential to know the extent of light propagation through living tissues of interest. This information can be obtained in an easy and exact way by using the phantom of the present invention.

Various modifications are possible with the present invention. For instance, physiological saline may be used instead of water as a medium in which polystyrene particles are to be suspended. If a light-absorbing dye is added in a suitable amount, the absorption characteristics of the phantom can be adjusted independently of its scattering characteristics.

As described in detail on the foregoing pages, a phantom having similar optical characteristics to living tissues of interest can be produced in the present invention by merely incorporating different-sized particles in a medium. Particularly high stability and reproducibility can be realized by selecting particles whose specific gravity is generally the same as that of the medium (for instance, by suspending polystyrene particles in water).

Claims

1. A phantom having similar optical characteristics to living tissues with respect to light-scattering characteristics, comprising:
a selected medium (2); and,
a mixture of particles (3) suspended in said medium, of different-valued radius r_k (k is a positive integer of 1 to m) at respective values of concentration C_k, wherein
said values of concentration C_k are determined on the basis of the following matrix equation.

$$\begin{bmatrix} P_{meas}(\theta_1) \\ \vdots \\ P_{meas}(\theta_i) \\ \vdots \\ P_{meas}(\theta_n) \end{bmatrix} = \begin{bmatrix} P(\theta_1, r_1) & \cdots & P(\theta_1, r_m) \\ \vdots & \ddots & \vdots \\ P(\theta_i, r_k) & & \\ \vdots & \ddots & \vdots \\ P(\theta_n, r_1) & \cdots & P(\theta_n, r_m) \end{bmatrix} \begin{bmatrix} C_1 \\ \vdots \\ C_k \\ \vdots \\ C_m \end{bmatrix}$$

where $P_{meas}(\theta_i)$ is a scattering intensity with said living tissues at a scattering angle θ_i (i is a positive integer of 1 to n) and $P(\theta_i, r_k)$ is a scattering intensity with said particles having said radius r_k at said scattering angle θ_i.

2. A phantom according to claim 1, wherein said values of concentration C_k are determined further on the basis of the following equation:

$$\mu_S = \sum_{k=1}^{m} C_k S_k$$

where μ_s is a reciprocal of a mean optical pathlength and S_k is a scattering cross-section of said particles of radius r_k.

3. A phantom according to claim 1 or 2, wherein said particles(3) have a specific gravity which is generally the same as that of said medium (2).

FIG. 1

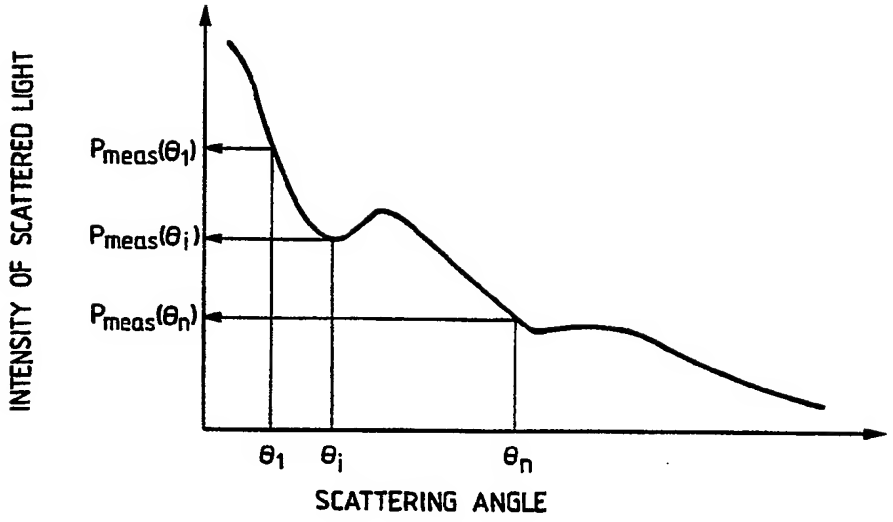


FIG. 2(a)

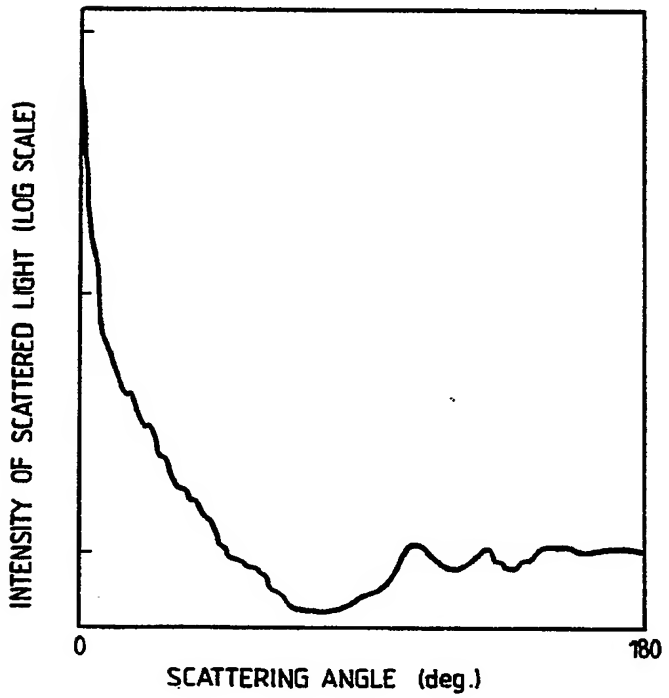


FIG. 2(b)

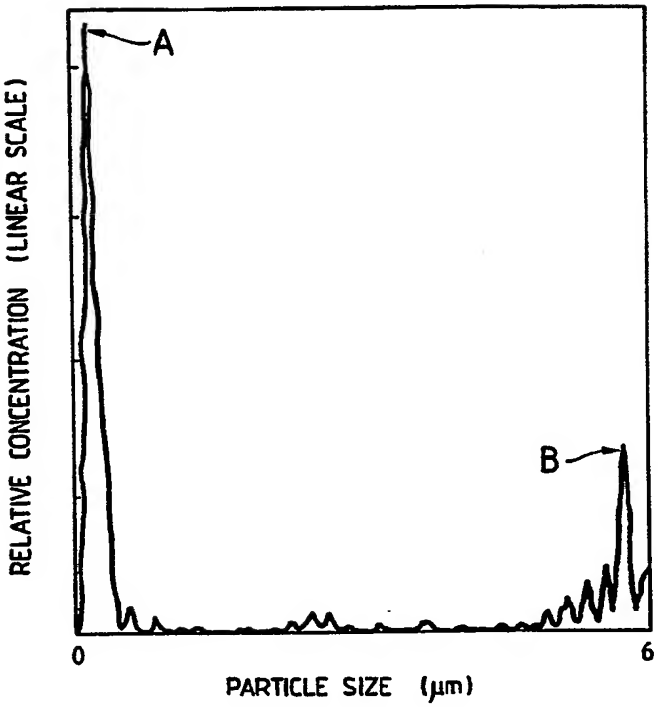


FIG. 2(c)

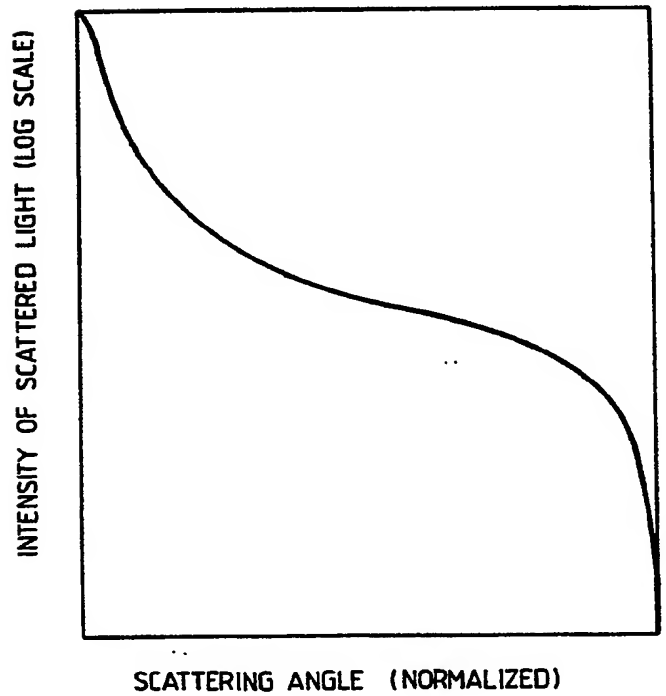


FIG. 2(d)

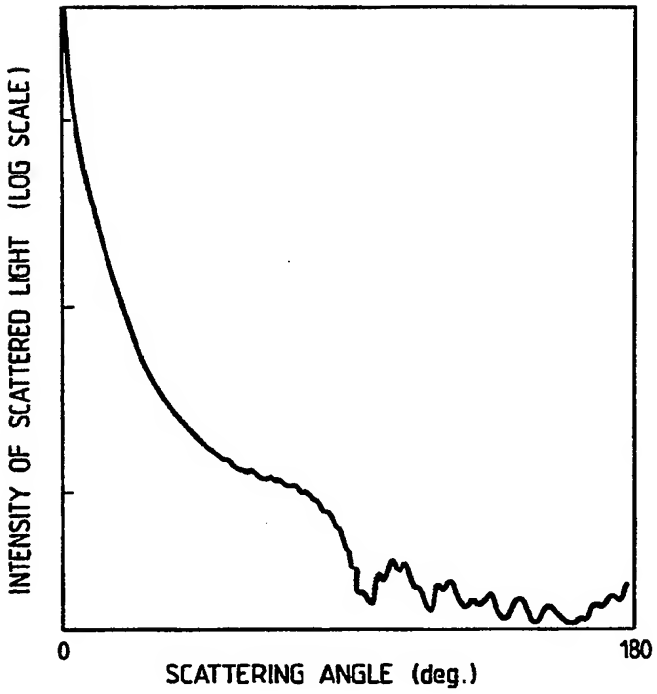


FIG. 3

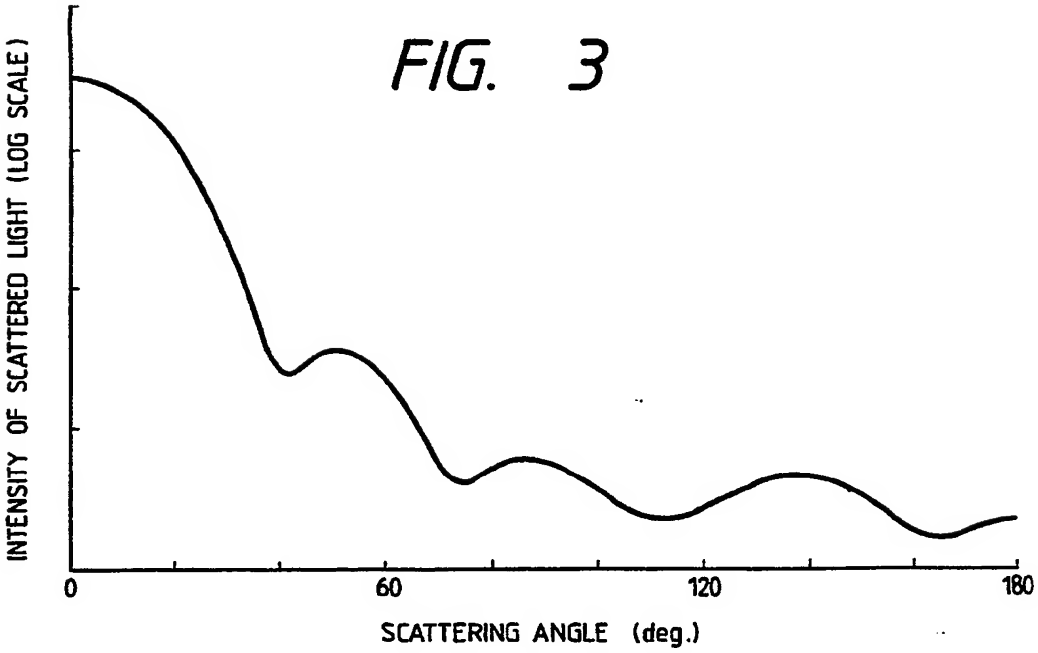


FIG. 4

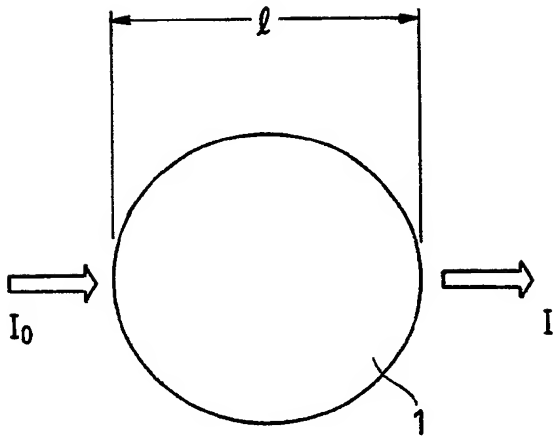
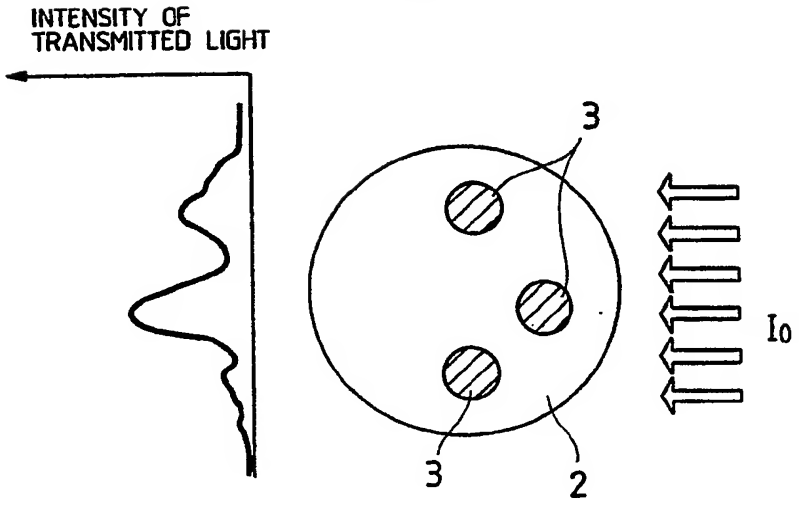


FIG. 5



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(54) Phantom having similar optical characteristics to living tissues.

(57) A phantom having similar light scattering characteristics to living tissues of interest is obtained by suspending in a selected medium (2) a mixture of particles (3) of different-valued radius r_k at respective values of concentration C_k which are determined on the basis of the following matrix equation:

$$\begin{bmatrix} P_{meas}(\theta_1) \\ \vdots \\ P_{meas}(\theta_i) \\ \vdots \\ P_{meas}(\theta_n) \end{bmatrix} = \begin{bmatrix} P(\theta_1, r_1) & \cdots & P(\theta_1, r_m) \\ \vdots & \ddots & \vdots \\ & P(\theta_i, r_k) & \\ \vdots & \ddots & \vdots \\ P(\theta_n, r_1) & \cdots & P(\theta_n, r_m) \end{bmatrix} \begin{bmatrix} C_1 \\ \vdots \\ C_k \\ \vdots \\ C_m \end{bmatrix}$$

where $P_{meas}(\theta_i)$ is a scattering intensity of light with the living tissues at a scattering angle θ_i and $P(\theta_i, r_k)$ is a scattering intensity with the particles having the radius r_k at the scattering angle θ_i.

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 30 4479

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	MEDICAL PHYSICS, vol. 14, no. 5, September 1987, pages 835-841, New York, US; S.T. FLOCK et al.: "Total attenuation coefficients and scattering phase functions of tissues and phantom materials at 633 nm" * Pages 837-838 * ---		G 01 N 21/47
A	PROCEEDINGS OF S.P.I.E., vol. 808: "Inverse Problems in Optics", 1987, pages 100-104, SPIE, Bellingham, WA, US; O. GLATTER et al.: "Size of shape analysis of elastic light scattering data from large particles (Mie scattering)" * Whole document * ---		
A	BRITISH JOURNAL OF APPLIED PHYSICS, vol. 3, no. 2, February 1970, pages 221-227; J.P. KRATOHVIL et al.: "Calibration of light-scattering photometers. VII. Calibration by means of colloidal dispersions of Mie scatterers" * Pages 221-222 * -----		TECHNICAL FIELDS SEARCHED (Int. Cl.5) G 01 N 21/47

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	07-02-1991	BOEHM CH.E.D.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
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O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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(54) Noninvasive method and apparatus for determining body chemistry

(57) The body chemistry of a person is determined by directing a beam of light into the eye (28) of the person, measuring the spectral response of the eye to the beam of light, comparing the measured spectral response to a standard spectral response, and forming a conclusion as to the chemistry of the body from the comparison. The light selected for the measurement does not harm the eye (28), and is preferably in the ultraviolet or infrared ranges. The response of the eye (28) chosen for measurement is that of reflected, fluoresced, or scattered light. It is preferred to use two or more of these techniques simultaneously, to minimize the likelihood of error. The comparison is made by comparing the measured response of the eye (28) to a standard response from a library of previously established responses.

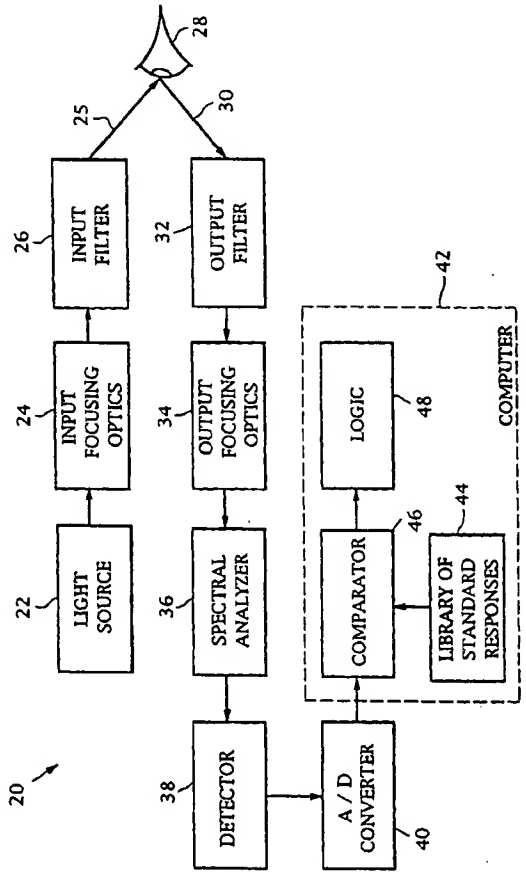

FIG. 1.

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Description

BACKGROUND OF THE INVENTION

This invention relates to the noninvasive measurement of body chemistry, and, more particularly, to the measurement of body chemistry using the response to light of externally accessible portions of the body.

The measurement of body chemistry is important in medicine, law enforcement, safety practice, and other fields. Body chemistry has traditionally been determined by obtaining fluid from the body, typically blood, urine, spinal fluid, and the like. A wet or spectral chemical analysis of the fluid is made and evaluated for the chemical content of the fluid.

In recent years, the effects of the use of illegal drugs such as narcotics and the excessive use of legal drugs such as alcohol have become important concerns for employers and others who may be affected by a person under the influence of such drugs. Drug testing programs, such as mandated testing for all prospective employees and random testing for persons in safety-sensitive positions, have become commonplace. Such testing is accomplished by obtaining fluid from the body and analyzing it as discussed previously. Apart from any question of legality of the testing, such testing is time consuming, expensive, invasive, and can cause physical discomfort or anxiety to some degree in those tested. The testing can also fail to achieve its desired objectives in some cases, as for example when a person has previously passed drug testing and thereafter uses an illegal drug shortly before performing a safety-sensitive function.

The majority of persons do not use drugs in an unacceptable manner. Invasive testing is, for those persons, a necessary burden both for those doing the testing and for the person tested. It would therefore be particularly desirable to have a reliable preliminary screening test to assess whether there was any reason to perform full quantitative testing in each case.

There is a need for an improved approach to determining body chemistry, such as the presence of drugs. Such an approach would desirably provide both a current state of body chemistry and information on the historical use of drugs, at least in a qualitative sense. The approach would also desirably be noninvasive, painless, and fast so as to reduce any burden associated with the testing. The present invention fulfills this need, and further provides related advantages.

SUMMARY OF THE INVENTION

The present invention provides a method and apparatus for performing a noninvasive determination of the body chemistry of a subject. The approach is versatile, and may be directed at those elements of body chemistry associated with body function and health, or those elements of body chemistry associated with the use or abuse of drugs, alcohol, and the like. The determination is performed quickly, without harm or physical discomfort to the subject, and without introducing any chemicals into the environment.

In accordance with the invention, a method for determining body chemistry comprises the steps of generating an input beam of light of a wavelength and intensity not harmful to an eye of a subject, directing the input beam of light into the eye of the subject, the step of directing being performed in vivo, and measuring a response, such as a spectral, scattering, or fluorescence response, of the eye to the input beam of light. The method further includes providing a standard spectral response of a chemical state of the eye to the input beam of light, comparing the measured spectral response to the standard spectral response, and forming a conclusion as to the body chemistry of the person from the comparison made in the step of comparing.

Measurements of body chemistry from the eye are useful because the eye is externally accessible and is physiologically insensitive to moderate intensities of particular wavelengths of light that can be easily generated and analyzed. Ultraviolet and infrared light are of particular interest for such determinations. Moreover, various regions of the eye have fluids therein whose composition changes either rapidly or slowly over time. Noninvasive measurements of the chemistry in these regions permits the body chemistry to be ascertained both for short-term and long-term effects.

In a preferred embodiment, multiple determinations of body chemistry are made simultaneously using the approach outlined above and separate light-based techniques. Thus, for example, obtaining reflectance, fluorescence, and scattering information at the same time, and at the same or different wavelengths, permits independent assessments of the body chemistry. Multiple determinations also allows logic to be applied in identifying various conditions such as false positive readings and abnormal responses to one type of test.

In accordance with the preferred embodiment, a method for determining body chemistry comprises the steps of generating an input beam of light of a wavelength and intensity not harmful to an eye of a subject, directing the input beam of light into the eye of the subject, the step of directing being performed in vivo, first measuring a first type of spectral response of the eye to the input beam of light, and second measuring a second type of response of the eye to the input beam of light. A first type and a second type of standard response of the eye to the input beam of light are provided, preferably in the form of a library of responses for various types of conditions and chemistries. The method further includes first comparing the measured first type of spectral response to the standard first type of response, second comparing the measured second type of response to the standard second type of response, and forming a conclusion as to the body chemistry of the person from the comparisons made in the steps of first and second com-

paring.

The present invention provides an advance in the art of determining the chemistry of the body. The method is fast, both in terms of requiring only a brief measuring period and also in terms of yielding the results quickly, and is noninvasive. Other features and advantages of the present invention will be apparent from the following more detailed description of the preferred embodiment, taken in conjunction with the accompanying drawings, which illustrate, by way of example, the principles of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic illustration of an apparatus according to the invention;

Figure 2 is a block diagram for practicing one embodiment of the method of the invention;

Figures 3(a) and 3(b) are idealized depictions of two sets of interrelations between the measured and standard spectral responses of the eye; and

Figure 4 is a schematic illustration of the eye in cross section, illustrating those parts pertinent to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Figure 1 schematically depicts a preferred apparatus 20 according to the invention, and Figure 2 shows the related method for practicing the invention using this apparatus 20. A light source 22 generates light that is used in the chemical analysis procedure, numeral 60. The light is of a wavelength and intensity that will not damage the eye, and, preferably, is not detected by the unaided eye. The light produced by the light source 22 is preferably at a wavelength of from about 200 to about 300 nanometers, in the ultraviolet range, and/or from about 700 to about 800 nanometers, in the near-infrared range. Both of these ranges are substantially undetected by the human eye, and does not damage the eye as long as the intensity is not so high or the duration of exposure so long that the light will damage the tissue.

Input focusing optics 24 directs an input beam 25 into the eye, numeral 62. The input focusing optics 24 is of a conventional type using lenses and mirrors, and may be adjustable to focus the light at specific locations within the eye, as will be discussed subsequently. An input filter 26 may also be provided to select specific wavelengths for introduction into the eye, inasmuch as the light source 22 may produce light of a bandwidth broader than that ultimately desired. Care is taken not to introduce a higher intensity or longer duration of light into the eye than required.

The focused and filtered input beam of light 25 is introduced into an eye 28 of a subject. The present invention is noninvasive except for this introduced beam, which is desirably not visible to the eye and does not harm the eye. (The term "noninvasive" as used herein means that there is no physical invasion of the body, but that introduction of a beam of light into the eye is permitted.) This chemical analysis is preferably accomplished in vivo, that is, with a live subject.

An output beam of light 30 is emitted from the eye 28 responsive to the stimulus of the input beam 25. The output beam 30 can be produced by various mechanisms within the eye, which will be discussed subsequently. The output beam 30 is optionally filtered by an output filter 32 if it is expected to contain wavelengths not of interest to the analysis. The output beam 30 passes through output focusing optics 34 of a conventional type to focus the output beam 30. At this point, the output beam 30 constitutes a single broadband beam. A spectral analyzer 36 breaks the output beam 30 into its component spectrum. The spectral analyzer 36 is desirably a prism, a diffraction grating, or a ruled grating.

The output focusing optics 34 is selected to focus the spectrally analyzed beam 36 onto a detector 38 having a bandwidth sufficient to encompass the wavelengths required for the subsequent analysis. The detector 38 receives as an input the filtered, focused, and analyzed output beam 30 and produces as an output an electrical signal indicative of the intensity of the input beam as a function of wavelength, termed a measured spectral response. If the detector 38 produces the measured spectral response in analog form and the subsequent procedures are to be performed digitally, as is preferably the case, an analog-to-digital (A/D) converter 40 is provided to make the conversion of the spectral response to digital form. On the other hand, if the output of the detector 38 is digital, as in the case of a charge-coupled diode array, then the A/D converter 40 would not be necessary.

The detector 38 can be a single detector or more that one detector for specific wavelengths. In the preferred embodiment, more than one response is analyzed. At least one of the responses is a spectral response in a selected wavelength range, and the other responses are typically either spectral responses in other wavelength ranges, fluorescence responses in a selected wavelength range, or scattering responses in a selected wavelength range. If these responses utilize, for example, both the ultraviolet and infrared wavelength ranges, separate detectors 38 for these ranges would ordinarily be provided. A beam splitter can be provided to direct components of the output beam to these detectors. The apparatus 32, 34, 36, 38, and 40 are collectively described as measuring a first response, numeral 64, and, where provided, a second response, numeral 64'.

The chemical analyses of the one or more responses are performed using the digital processing capabilities of a computer 42 and a library 44 of standard response(s) stored in the computer.

The measured spectral response can be characterized in various ways. Most commonly, the spectral response is a curve of intensity as a function of wave-

length, as depicted in Figures 3(a) and 3(b). Such a curve typically exhibits peaks indicative of the chemical composition of the region of the eye 28 in which the input beam 25 interacts with the liquid inside the eye to produce the output beam 30. The spectral response of this type can therefore be alternatively characterized by the wavelengths of the peaks found in the spectrum.

Standard spectral responses for various possible chemical constituents of the body are provided, numeral 66 (and, where appropriate, 66'). These standard spectral responses are, in many cases, available in reference works. If not, a standard spectral response can be developed by preparing a simulated subject eye having a fluid therein which contains a known chemical of interest in a known concentration. The apparatus 20 is used to measure the spectral response of this known standard, which then becomes part of the standard spectral response library for subsequent measurements of unknowns. The present approach can be used with just a single standard response in the library of each type of spectral response, if there is an interest in analyzing for just one chemical type. On the other hand, in the drug-screening application, a number of standard spectral responses--each corresponding to the response characteristic of an illegal drug--is provided in the library. The screening for multiple chemicals requires no further testing of the subject, only additional repetitions of the computer matching operation.

The measured spectral response, provided from the detector 38, and the standard spectral response for a particular chemical, provided from the library, are compared, numeral 68 (and 68') by a comparator function 46 in the computer 42. Many analog and digital techniques for comparing two curves for a goodness of correlation are available, and any of these techniques can be used. In the preferred approach, the comparison is performed digitally. The preferred technique is to prepare a listing of the peaks found in the measured and standard spectral responses, using a cutoff value to differentiate a peak from the background. Then the presence and absence of peaks in the measured and standard spectral responses is compared to find the degree to which the measured spectral response matches to the standard spectral response for each chemical being studied. Thus, the preferred approach involves matching peak locations, rather than peak locations and peak intensities by more-mathematical approaches such as autocorrelation, because of variations in concentration of the chemicals between the measured specimen and the standard.

Once a degree of matching, ranging from none to perfect, of the measured and the standard spectral responses is determined in step 68 is available, logic 48 is applied to form a conclusion as to the presence or absence of the chemical in the subject, numeral 70. At the limits of no or perfect matching, there is no difficulty in determining the absence or presence, respectively, of the chemical used to prepare the standard. In other cases, however, the identification can be more difficult.

Figures 3(a) and 3(b) illustrate some of the possible situations. In Figure 3(a), there is a clear match of two of three peaks, but not a clear match as to the third peak. In a case such as this, it may be useful to have a measured spectral response of another type, and the preferred embodiment of Figure 2 provides for the use of multiple types of spectral responses to improve the certainty of identification. In Figure 3(b), two different standard spectral responses are required to account for all of the peaks of the measured spectral response, suggesting that the chemicals associated with the spectral responses of both standards are present. There can be no generalization as to the analysis of various spectral responses, and each individual case must be handled separately.

At the present time, three types of responses of the eye are contemplated for use with the invention, although the invention is not limited to these three and others can be used. All of these techniques are known to be operable for the detection of chemicals such as drugs, using other types of instrumentation. See, for example, W.F. Ulrich et al., "Analytical Instrumentation in the Forensic Sciences," Beckman Instruments Corp., May 1971.

The first type of analysis is ultraviolet reflection (ultraviolet spectrophotometry) to measure the absorption spectrum. This measurement is conducted with input light of about 200-300 nanometers wavelength and output light of the same wavelength range. The second type of analysis is ultraviolet fluorescence. This measurement is conducted with input light of a specific wavelength within the range of about 200-300 nanometers, and output light and subsequent spectral data curves in the range of 300 nanometers and above, and typically in the range of about 300-500 nanometers. The same ultraviolet light source may be used for both reflection and fluorescence, but the detector has a range of about 200-300 nanometers for reflection and 300-500 nanometers for fluorescence. Many UV reflection and fluorescence spectral response curves are available in the scientific and medical literature.

The third type of spectral analysis is Raman infrared scattering spectroscopy of light in the range of about 700 to about 800 nanometers. Both a different light source 22 and a different detector 38 are ordinarily used for the infrared measurements than for the UV measurements. Light sources and detectors for both the UV and IR ranges are readily available commercially. As in the case of the UV spectroscopy, Raman spectra of various drugs and other chemicals are available in the scientific and medical literature.

Figure 4 schematically illustrates that portion of the structure of the human eye which is pertinent to the present invention. The eye 28 is generally, but not perfectly, spherical. It is received in a socket 80 in the skull. Tear glands and ducts 82 in the soft tissue surrounding the socket produce moisture that covers the front sur-

face of the eyeball with a thin film 84 of tears. A cornea 86 lies behind the tear surface of the eye, and a lens 88 is spaced apart behind the cornea. Between the cornea 86 and the lens 88 lies a volume of fluid termed the aqueous humor 90. Behind the lens 88 lies a volume of fluid termed the vitreous humor 92.

There are thus three distinct volumes of fluid associated with the eye 28: the tears 84, the aqueous humor 90, and the vitreous humor 92. The optics 24 and 34 of the present invention are designed to obtain spectral responses from these three areas individually. The advantage to obtaining responses from the areas one at a time is that the fluid in each volume is changed at a different rate by the body. The tears 84 are produced with fluid that changes about every 5-7 minutes. The fluid of the aqueous humor 90 changes about every 1-1/2 to 2 hours. The fluid of the vitreous humor 92 changes over a matter of days.

An optical response analysis of the tears therefore indicate the current status of a chemical found in the tears. The optical spectral response analysis of the aqueous humor provides a 1-1/2 to 2 hour average of a chemical found in the fluid of the aqueous humor. The optical spectral response analysis of the vitreous humor provides a longer term average of a chemical found in the fluid of the vitreous humor. The ability to selectively obtain current or time-averaged data on the presence of chemicals from a single test procedure, changing nothing more than the focus of the optical components, is of value to those seeking the presence of drugs in the system of the subject, and also to medical personnel studying normal and abnormal functioning of the body.

The chemical composition of each selected region of the eye can be sampled by controlling the optics 24 and 34 of the apparatus 20, leaving the other elements unchanged. To sample a selected region, the focal lengths of the input focusing optics 24 and the output focusing optics 34 are set to the required values to focus in the selected region of the eye. Responses of the eye are thence the responses of the selected region.

At the present time, the invention is designed for use in a qualitative manner to detect the presence of chemicals that might require further detailed sampling and chemical analysis. The present approach requires only about one second to provide a screening of the subject as to complete absence of a chemical in the fluid of the eye, or the presence of a quantity of the chemical that could require further sampling and analysis to establish an exact quantitative value of the chemical.

The discussion herein has been directed primarily toward the detection of illegal drugs, the principal interest of the inventor. The present invention is not so limited, however. It may be used for medical applications such as sugar in diabetics and chemically based diseases of the eye.

Although a particular embodiment of the invention has been described in detail for purposes of illustration, various modifications and enhancements may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not to be limited except as by the appended claims.

Claims

1. A method for determining body chemistry, comprising the steps of:

   generating an input beam of light of a wavelength and intensity not harmful to an eye of a subject;
   directing the input beam of light into the eye of the subject, the step of directing being performed in vivo;
   measuring a response of the eye to the input beam of light;
   providing a standard response of a chemical state of the eye to the input beam of light;
   comparing the measured response to the standard response; and
   forming a conclusion as to the body chemistry of the person from the comparison made in the step of comparing.

2. The method of claim 1, wherein the step of generating includes the step of

   generating light of a wavelength selected from the group consisting of a wavelength of from about 200 to about 300 nanometers and from about 700 to about 800 nanometers.

3. The method of claim 1, wherein the step of directing includes the step of

   focusing the input beam of light to a selected location within the eye.

4. The method of claim 1, wherein the step of directing includes the step of

   filtering the input beam of light to remove wavelengths that are not within a desired wavelength range.

5. The method of claim 1, wherein the step of measuring includes the step of

   focusing an output beam of light from the eye upon a spectral detector.

6. The method of claim 5, wherein the step of focusing includes the step of

   focusing the output beam of light from a layer of a tearing fluid on an external surface of the

eye.

7. The method of claim 5, wherein the step of focusing includes the step of

focusing the output beam of light from an aqueous humor of the eye.

8. The method of claim 5, wherein the step of focusing includes the step of

focusing the output beam of light from a vitreous humor of the eye.

9. The method of claim 1, wherein the step of generating includes the step of

generating an input beam having a wavelength of from about 200 to about 300 nanometers; and wherein the step of measuring includes the step of
measuring a reflected beam of light.

10. The method of claim 1, wherein the step of generating includes the step of

generating an input beam having a wavelength of from about 200 to about 300 nanometers; and wherein the step of measuring includes the step of
measuring a fluoresced beam of light.

11. The method of claim 1, wherein the step of generating includes the step of

generating an input beam having a wavelength of from about 700 to about 800 nanometers; and wherein the step of measuring includes the step of
measuring a scattered beam of light.

12. The method of claim 1, further including the additional steps of

second measuring a second type of response of the eye to the input beam of light;
second providing a second type of standard response of the eye to the input beam of light;
second comparing the measured second type of response to the standard second type of response; and wherein the step of forming a conclusion includes the step of
forming the conclusion as to the body chemistry of the person from the comparisons made in the steps of comparing and second comparing.

13. Apparatus for determining body chemistry, comprising:

a source of an input beam of light of a wavelength and intensity not harmful to an eye of a subject;
a beam director which receives the input beam of light and directs the input beam into the eye of the subject;
a detector system that measures a measured response of the eye to the input beam of light;
a source of a standard response of a chemical state of the eye to the input beam of light;
a comparator which compares the measured response to the standard response; and
a logic circuit which reaches a conclusion as to the body chemistry of the person from the comparison made by the comparator.

14. The apparatus of claim 13, further including

a second detector system that measures a measured second response of the eye to the input beam of light,
a source of a standard second response of a chemical state of the eye to the input beam of light, and
a second comparator which compares the measured second response to the standard second response; and wherein the logic circuit includes
a logic circuit which reaches a conclusion as to the body chemistry of the person from the comparison made by the comparator and the second comparator.

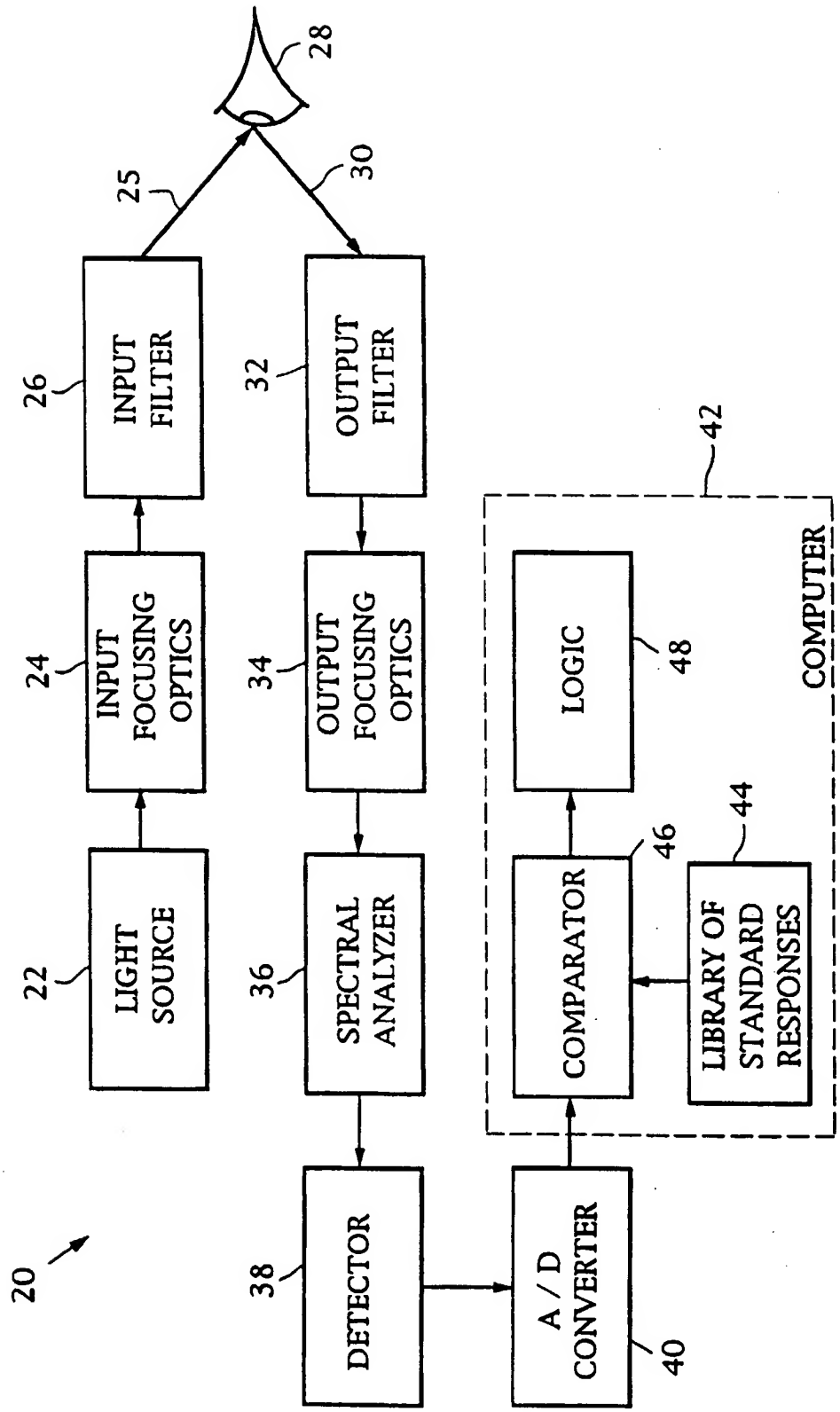

20
22
LIGHT SOURCE
24
INPUT FOCUSING OPTICS
26
INPUT FILTER
25
28
30
32
OUTPUT FILTER
34
OUTPUT FOCUSING OPTICS
36
SPECTRAL ANALYZER
38
DETECTOR
40
A / D CONVERTER
42
COMPUTER
46
COMPARATOR
48
LOGIC
44
LIBRARY OF STANDARD RESPONSES

FIG. 1.

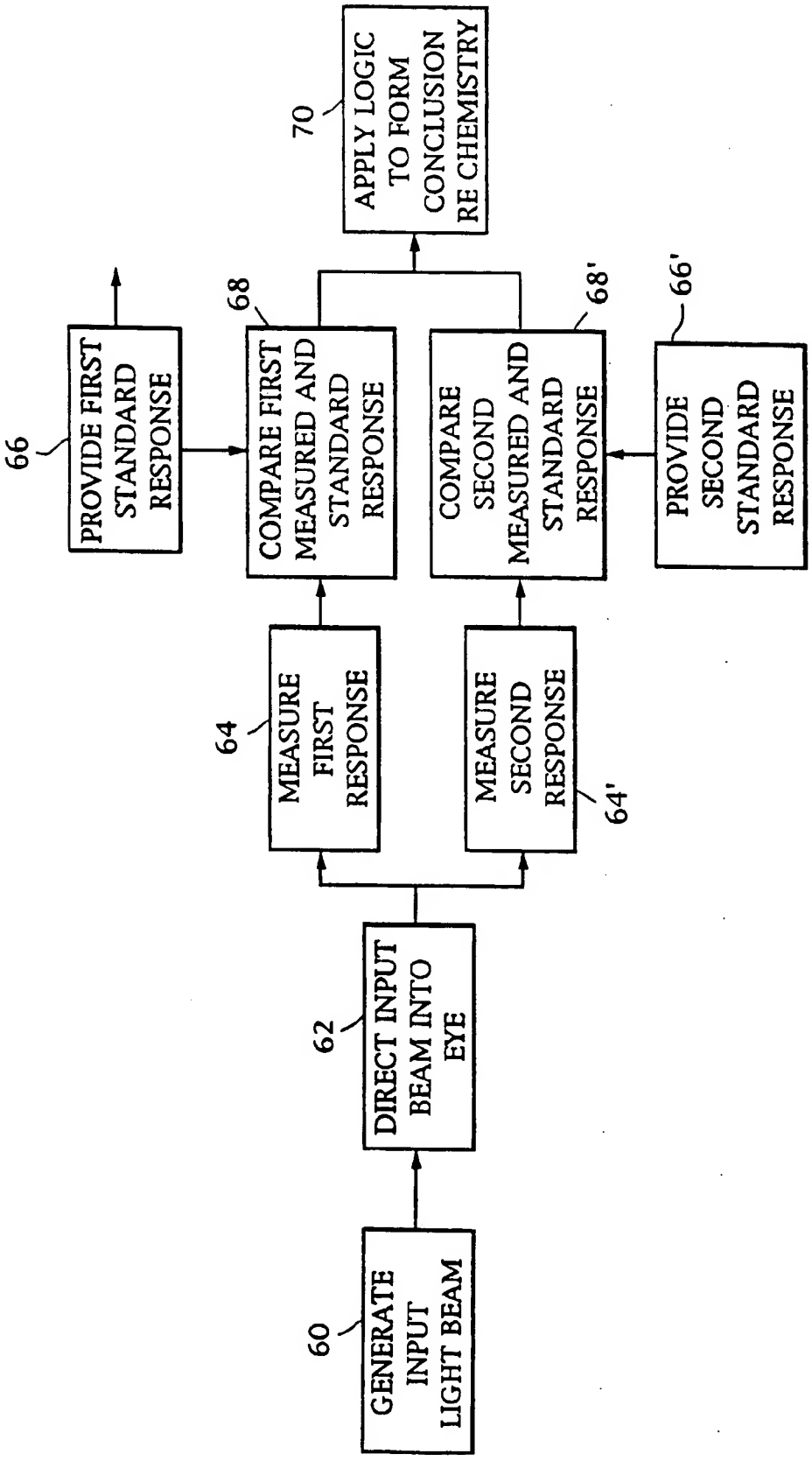

GENERATE INPUT LIGHT BEAM
60
DIRECT INPUT BEAM INTO EYE
62
MEASURE FIRST RESPONSE
64
MEASURE SECOND RESPONSE
64'
PROVIDE FIRST STANDARD RESPONSE
66
PROVIDE SECOND STANDARD RESPONSE
66'
COMPARE FIRST MEASURED AND STANDARD RESPONSE
68
COMPARE SECOND MEASURED AND STANDARD RESPONSE
68'
APPLY LOGIC TO FORM CONCLUSION RE CHEMISTRY
70

FIG. 2.

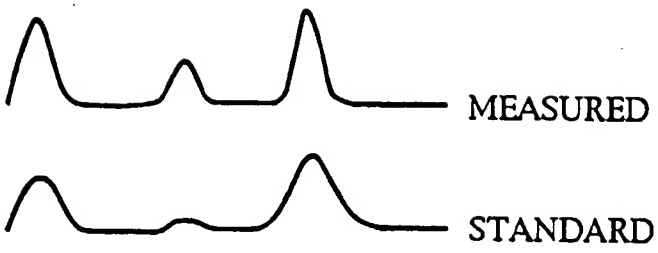


FIG. 3(a)

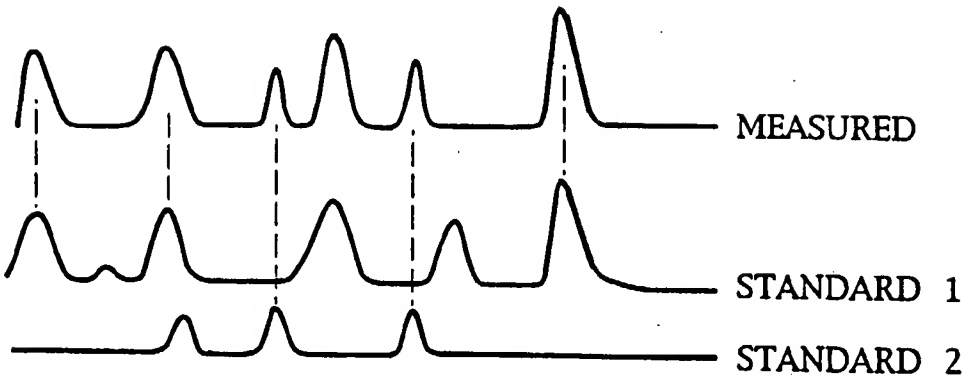


FIG. 3(b)

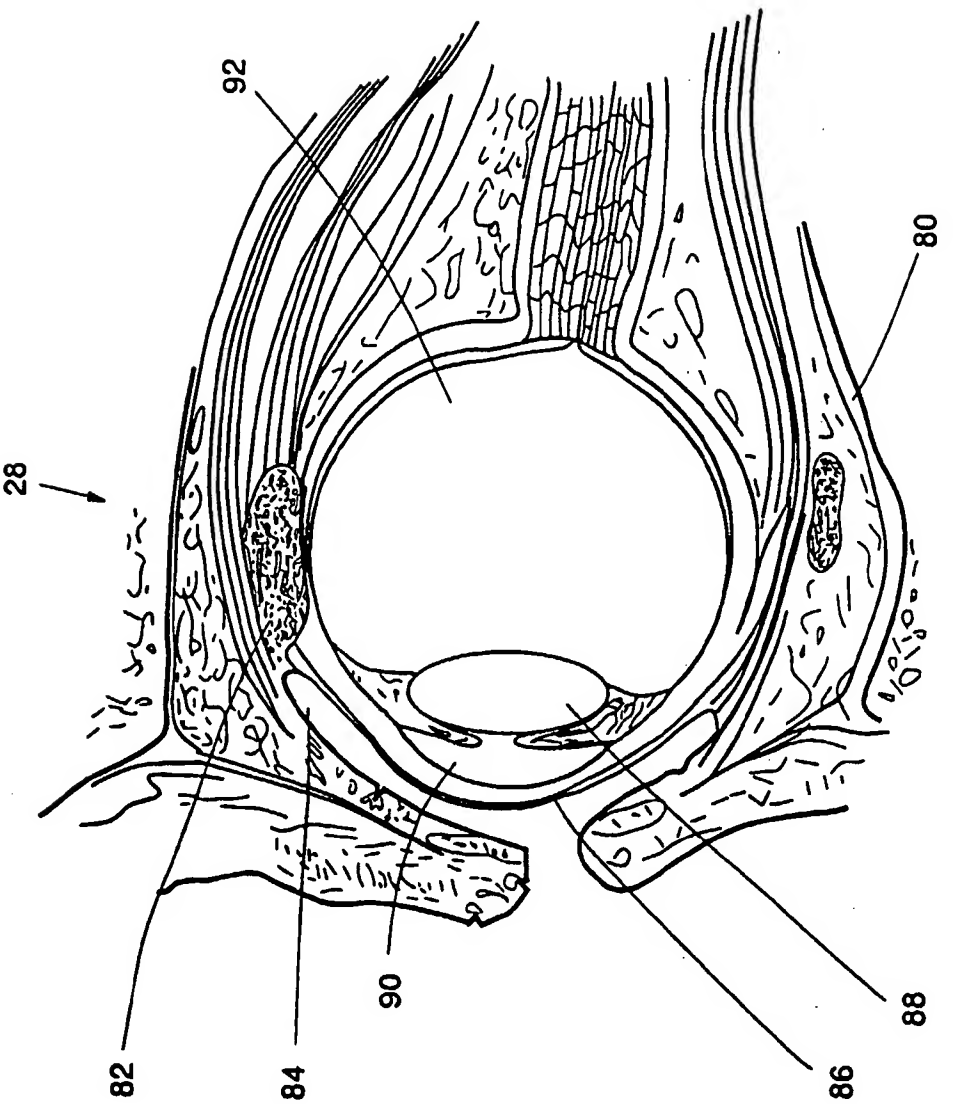


FIG. 4.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 30 0098

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP-A-0 589 191 (W.EDWARD STARK)	1-9,11, 13	A61B5/00
A	* abstract * * column 6, line 15 - column 13, line 52; tables 1-7 *	12,14	
X	DE-A-31 17 699 (METRICON, LTD.)	1	
A	* page 14, line 16 - page 19, line 13; tables 1,2 *	10	
X	DE-A-42 43 142 (BOEHRINGER MANNHEIM GMBH)	1-5,7,9, 13	
A	* column 3, line 40 - column 4, line 39 * * column 4, line 58 - column 9, line 7; tables 1-5 *	11	
X	WO-A-93 07801 (SCIENTIFIC GENERICS LIMITED)	1,3,5,6	
A	* page 12, line 19 - page 15, line 6; table 1 *	2,4	
X	US-A-3 963 019 (ROBERT S. QUANDT) * abstract; tables 1,2 *	1	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61B

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	26 March 1996	Weihs, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

METHOD AND APPARATUS FOR NONINVASIVE MEASUREMENT OF CAROTENOIDS AND RELATED CHEMICAL SUBSTANCES IN BIOLOGICAL TISSUE

Publication number: JP2003507088 (T)
Publication date: 2003-02-25
Inventor(s):
Applicant(s):
Classification:
- international: ***A61B5/00; A61B10/00; G01N21/65;*** **A61B5/00; A61B10/00; G01N21/63;** (IPC1-7): A61B10/00; G01N21/65
- European: A61B5/00P; G01N21/65
Application number: JP20010504288T 20000322
Priority number(s): US19990335932 19990618; WO2000US07745 20000322

Also published as:
JP3786873 (B2)
WO0078217 (A1)
US6205354 (B1)
KR100825521 (B1)
KR20070004144 (A)
more >>

Abstract not available for JP 2003507088 (T)
Abstract of corresponding document: **WO 0078217 (A1)**

A method and apparatus are provided for the determination of levels of carotenoids and similar chemical compounds in biological tissue such as living skin (34). The method and apparatus provide a noninvasive, rapid, accurate, and safe determination of carotenoid levels which in turn can provide diagnostic information regarding cancer risk, or can be a marker for conditions where carotenoids or other antioxidant compounds may provide diagnostic information.

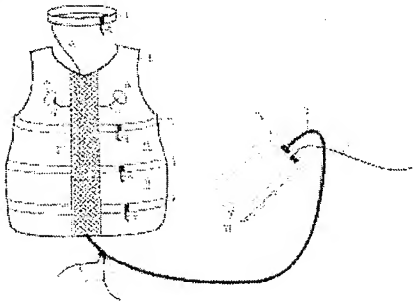
SYSTEMS AND METHODS FOR AMBULATORY MONITORING OF PHYSIOLOGICAL SIGNS

Publication number: JP2003530184 (T)
Publication date: 2003-10-14
Inventor(s):
Applicant(s):
Classification:
- international: ***A61B5/00; A61B5/0205; A61B5/0245; A61B5/0404; A61B5/0408; A61B5/0436; A61B5/0478; A61B5/08; A61B5/11; A61B5/113; A61B5/145;*** *A61B5/0432; A61B5/103; A61B7/00;* **A61B5/00; A61B5/0205; A61B5/024; A61B5/0402; A61B5/0408; A61B5/0432; A61B5/0476; A61B5/08; A61B5/11; A61B5/145;** A61B5/103; A61B7/00; (IPC1-7): A61B5/00; A61B5/0245; A61B5/0404; A61B5/0408; A61B5/0436; A61B5/0478; A61B5/08; A61B5/11; A61B5/145
- European: A61B5/0205; A61B5/113B
Application number: JP20010575884T 20010417
Priority number(s): US20000197589P 20000417; WO2001US12488 20010417

Also published as:
WO0178577 (A2)
WO0178577 (A3)
EP1296591 (A2)
EP1296591 (A4)
CA2405848 (A1)
more >>

Abstract not available for JP 2003530184 (T)
Abstract of corresponding document: **WO 0178577 (A2)**

The present invention relates to the field of ambulatory and non-invasive monitoring of a plurality of physiological parameters of a monitored individual. The invention includes a physiological monitoring apparatus with an improved monitoring apparel worn by a monitored individual, the apparel having attached sensors for monitoring parameters reflecting pulmonary function, or parameters reflecting cardiac function, or parameters reflecting the function of other organ systems, and the apparel being designed and tailored to be comfortable during the individual's normal daily activities. The apparel is preferably also suitable for athletic activities.; The sensors preferably include one or more ECG leads and one of more inductive plethysmographic sensors with conductive loops positioned closely to the individual to preferably monitor at least basic cardiac parameters, basic pulmonary parameters, or both. The monitoring apparatus also includes a unit for receiving data from the sensors, and for storing the data in a computer-readable medium. The invention also includes systems comprising a central data repository for receiving, storing, and processing data generated by a plurality of physiological monitored apparatuses, and for making stored data available to the individual and to the health care providers.

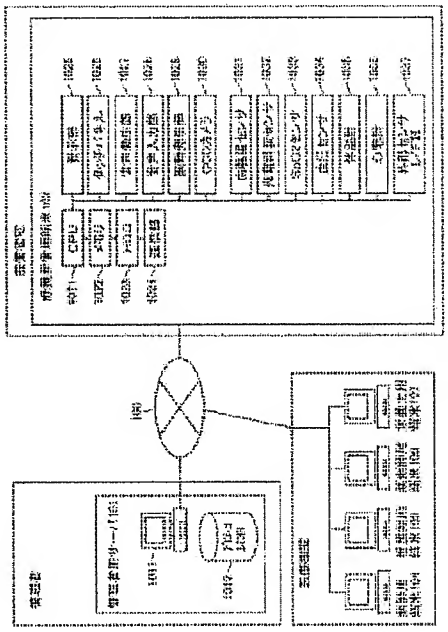


HOME TREATMENT PATIENT SUPPORTING SYSTEM AND METHOD

Publication number: JP2003108679 (A)
Publication date: 2003-04-11
Inventor(s): SUZUKI TAKUJI; KANAYAMA SHOICHI +
Applicant(s): TOSHIBA CORP +
Classification:
- international: ***A61B5/00; A61B5/022; A61B5/0245; A61B5/04; A61B5/0402; A61B5/11; A61B5/145; A61B5/1455; A61G12/00; G06Q50/00;*** **A61B5/00; A61B5/022; A61B5/024; A61B5/04; A61B5/0402; A61B5/11; A61B5/145; A61G12/00; G06Q50/00;** (IPC1-7): G06F17/60; A61B5/00; A61B5/022; A61B5/0245; A61B5/04; A61B5/0402; A61B5/11; A61B5/145; A61G12/00
- European:
Application number: JP20010303428 20010928
Priority number(s): JP20010303428 20010928

Abstract of **JP 2003108679 (A)**

PROBLEM TO BE SOLVED: To provide a home treatment patient supporting system capable of providing fine home treatment support to a home treatment patient having a risk such as lifestyle related diseases. SOLUTION: This home treatment patient supporting system is constituted of a server 101 for a manager set at a manager (service agent) side, and a patient residence managing terminal 102 set at a recuperator's house, and a terminal for a person in charge of a medical care, that is, a terminal 104 for a doctor, a terminal 105 for a nurse, a terminal 106 for a pharmacist, and a terminal 107 for a dietitian set in a medical facility, which are connected through a public line (or WAN) 100 to each other. The recuperater managing terminal 102 is provided with a function for interacting with the patient, a function for acquiring the biological information of the patient, and a function for transmitting information to the medical institution. The server 101 for the manager is provided with a terminal 1011 for the manager and a protocol data base (DB) 1012.



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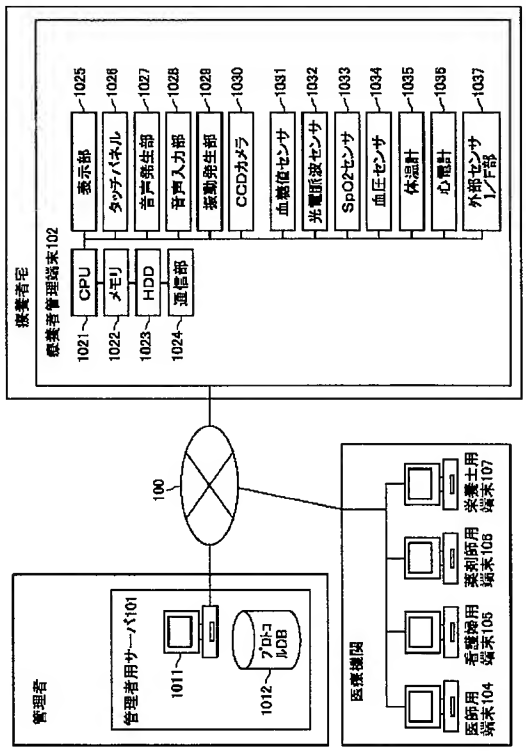
(54)【発明の名称】　在宅療養者支援システムおよび方法

(57)【要約】
【課題】　生活習慣病などのリスクを持つ在宅療養者に対してきめ細かな在宅療養支援が可能な在宅療養者支援システムを提供する。
【解決手段】　在宅療養者支援システムは、管理者（サービス事業者）側に設けられた管理者用サーバ１０１と、療養者宅に設けられた療養者管理端末１０２と、医療機関に設けられた医療従事者用端末、即ち、医師用端末１０４、看護婦用端末１０５、薬剤師用端末１０６、及び栄養士用端末１０７とが、公衆回線（あるいはＷＡＮ）１００にて接続されて構成されている。療養者管理端末１０２は、療養者との対話機能、療養者の生体情報の取得機能及び医療機関への情報伝送機能を有する。管理者用サーバ１０１には、管理者用端末１０１１とプロトコルデータベース（ＤＢ）１０１２とが設置される。



【特許請求の範囲】
【請求項１】　医療従事者が療養者に関する個人情報及び医療情報を入力するための医療従事者用端末と、
この医療従事者用端末にて入力された前記療養者の個人情報及び医療情報に基づいて前記療養者の在宅療養のための行動スケジュールを規定する動作プロトコルを生成又は修正する動作プロトコル生成手段と、
前記生成又は修正された動作プロトコルに従って前記療養者に在宅療養のための行動スケジュールを呈示すると共に前記療養者の応答を入力するマンマシンインタフェース、前記療養者の生体情報を取得するセンサ及び前記センサで取得された生体情報を前記医療従事者用端末に送信する通信手段を有する療養者管理端末とを具備してなることを特徴とする在宅療養者支援システム。
【請求項２】　前記医療従事者用端末から入力される医療情報は、投薬指示、運動指示、リハビリテーションメニュー及び生体情報計測指示の少なくとも１つを含み、前記療養者管理端末が呈示する行動スケジュールは、前記投薬指示、運動指示、リハビリテーションメニュー及び生体情報計測指示の少なくとも１つに基づく服薬指示メッセージ、運動指示メッセージ、リハビリテーション指示メッセージ及び生体情報計測指示メッセージの少なくとも１つを含むことを特徴とする請求項１記載の在宅療養者支援システム。
【請求項３】　前記医療従事者用端末は、医師用端末、看護婦用端末、薬剤師用端末及び栄養士用端末を含み、前記動作プロトコル生成手段は、前記医療従事者用端末から入力された医療情報に基づき生成される行動スケジュールに不整合が生じたときに、これを前記医療従事者に報知して修正を促すものであることを特徴とする請求項１又は２記載の在宅療養者支援システム。
【請求項４】　前記動作プロトコル生成手段は、前記療養者管理端末からの療養者の応答に基づいて前記動作プロトコルを適宜修正するものであることを特徴とする請求項１～３のいずれか１項記載の在宅療養者支援システム。
【請求項５】　前記療養者の行動を検出する行動検出手段を更に備え、前記動作プロトコル生成手段は、前記行動検出手段による前記療養者の行動の検出結果に基づいて前記動作プロトコルを適宜修正するものであることを特徴とする請求項１～３のいずれか１項記載の在宅療養者支援システム。
【請求項６】　前記療養者の特定の生体情報の真値又は真値として扱われているデータと、前記療養者管理端末での計測結果とが一致するような前記療養者管理端末のパラメータを計算する手段と、
前記パラメータを前記療養者管理端末に設定する手段とを更に具備することを特徴とする在宅療養者管理システム。
【請求項７】　医療従事者が医療従事者用端末に療養者に関する個人情報及び医療情報を入力するステップと、
前記入力された療養者の個人情報及び医療情報に基づいて前記療養者の在宅療養のための行動スケジュールを規定する動作プロトコルを生成又は修正するステップと、
前記生成又は修正された動作プロトコルに従って、療養者管理端末に前記療養者の在宅療養のための行動スケジュールを呈示するステップと、
前記療養者管理端末に対する療養者の応答を入力するステップと、
前記療養者管理端末に設けられたセンサで前記療養者の生体情報を取得するステップと、
センサ及び前記センサで取得された生体情報を前記医療従事者用端末に送信するステップとを具備してなることを特徴とする在宅療養者支援方法。
【発明の詳細な説明】
【０００１】
【発明の属する技術分野】本発明は、生活習慣病などのリスクを持つ在宅療養者の健康管理や疾病の治療をネットワークを介して行う在宅療養者支援システムおよび方法に関する。
【０００２】
【従来の技術】現代の主要死因である心筋梗塞などの心臓病、脳梗塞などの脳血管疾患などは生活習慣病とよばれ、これらのほとんどが高血圧、糖尿病、脂質代謝異常、肥満、喫煙などによってもたらされる動脈硬化が原因である。高血圧、糖尿病、脂質代謝異常など高リスク状態が健康診断により診断された場合、特に症状が出ないため、日常生活を送りながら指示された頻度、時間での血糖など生体情報の計測、処方されたとおりの薬品の服用、指示された運動、食事などの生活管理を行うことが多い。生活習慣病ではこれら生活管理がもっとも重要な治療となる。しかし実際は日常生活での忙しさや怠慢でこれを十分に自己管理できないために症状を悪化させてしまうことが非常に多い。一方これらの処方を行う医師や薬剤師、栄養士などの医療従事者は、治療のためのさまざまな指導を行うが、患者の日常生活の中で実際に実施されているかいちいち確認するなどの管理は時間的に非常に困難であった。また様々な機関の様々な職種のスタッフがそれぞれの指示、処方を行うが、療養者から見ると、それらを一日の生活のなかでどのような手順でこなしていったらいいか理解できず、服薬や計測を忘れてしまうなど、管理が十分に達成されないことが多い。
【０００３】現在でも患者宅に健康管理端末を置き、在宅で健康管理を行うシステムやサービスはすでに行われている。例えば、MediData（商標：セコム株式会社）などがこれに相当する。この端末は患者の体温、脈拍、血圧、血糖などのバイタルサインを計測するセンサを持ち、これらを用いて計測したデータをネットワークを介して契約医師に送信する。またタッチパネル画面を持ち簡単な問診のメニューが表示され、これに「はい」「い

いえ」のような入力を行い、これらのデータもあわせて医師に送信する。医師は送られたデータを診断し、生活指導などを行う。

【0004】

【発明が解決しようとする課題】しかし、これら従来の在宅健康管理サービス機器では、担当医師が固定になっており、投薬などの処方だけでなく、栄養指導、運動療法など細かいところまで処方をする必要もあるだけでなく、端末側の計測のスケジューリングや問診内容までも作成しており、これらの細かい条件まで医師が決めなければならず、これは大変な負担であった。また入力／操作などのヒューマンインターフェイスはタッチパネルのみであり、糖尿病などによる失明や弱視の患者が使用するのが非常に困難であった。在宅療養者は失明、難聴など身体的に障害を持つ場合も多く、患者すべてが簡単に使用できるようなヒューマンインターフェイスの実現は非常に困難であった。また問診での入力は自己申告であり、医師へ生活パターンを報告するため、頻度が少なく情報が欠落したり虚偽になる場合が多く、正確な処方が難しかった。

【0005】一方、被検体内に存在する物質の成分や濃度を測定するための代表的な従来装置としては、血液中もしくは体液中のグルコース濃度（血糖値）を測定する血糖計がある。現在広く用いられている血糖計は、被検体の指や腕などの部位の一部に針を刺して採取した少量の血液サンプルを利用するもので、この採取した血液中のグルコースを化学反応させてその濃度を測定する。このような採血式の血糖計は携帯可能な大きさであり、糖尿病患者の血糖値の管理に利用されている。さらに、これらの装置の問題である被検者の皮膚損傷や苦痛を軽減する目的で、微小な針やレーザを用いて痛みを伴わない程度の微小な穴を皮膚表面に開け微量の細胞間質液を採取して測定する方法や、皮膚表面に電圧や超音波を印加して皮膚の浸出透過性を良くし細胞間質液等の浸出液を抽出して測定する方法等が研究されている。また、唾液あるいは歯肉溝液を微量採取し血糖値を測定する方法も研究されている。

【0006】また、グルコース等の被検体内に存在する物質の成分や濃度を採血や細胞間質液の抽出を必要せずに非侵襲で測定する方法としては、特公平3－47099号公報あるいは特公平5－58735号公報に示されているような電磁波を利用した方法がある。これらは近赤外光、可視光を用いた生体物質の非侵襲分光分析方法であり、近年注目されている方法である。このような方法では照射した電磁波の反射波、あるいは透過波を計測し、測定する対象の物質の特性に合わせたパラメータを用いて解析的にその成分や濃度を求めている。パラメータは通常、採血などで得られた値を元にキャリブレーションにより求められる。パラメータは患者の状態等経時的な変化によりこまめな再キャリブレーションが必要であるが、このようなメンテナンスをサービス提供側である医師等が自ら行うのは煩雑でもあり、医師本来の業務以外の負担を増加させることになり、非常に非効率的であった。

【0007】本発明は、このような点に鑑みなされたもので、生活習慣病などのリスクを持つ在宅療養者に対してきめ細かな在宅療養支援が可能な在宅療養者支援システム及び方法を提供することを目的とする。

【0008】

【課題を解決するための手段】上記課題を解決するため、本発明の在宅療養者支援システムは、医療従事者が療養者に関する個人情報及び医療情報を入力するための医療従事者用端末と、この医療従事者用端末にて入力された前記療養者の個人情報及び医療情報に基づいて前記療養者の在宅療養のための行動スケジュールを規定する動作プロトコルを生成又は修正する動作プロトコル生成手段と、前記生成又は修正された動作プロトコルに従って前記療養者に在宅療養のための行動スケジュールを呈示すると共に前記療養者の応答を入力するマンマシンインタフェース、前記療養者の生体情報を取得するセンサ及び前記センサで取得された生体情報を前記医療従事者用端末に送信する通信手段を有する療養者管理端末とを具備してなることを特徴とする。

【0009】また、本発明に係る在宅療養者支援方法は、医療従事者が医療従事者用端末に療養者に関する個人情報及び医療情報を入力するステップと、前記入力された療養者の個人情報及び医療情報に基づいて前記療養者の在宅療養のための行動スケジュールを規定する動作プロトコルを生成又は修正するステップと、前記生成又は修正された動作プロトコルに従って、療養者管理端末に前記療養者の在宅療養のための行動スケジュールを呈示するステップと、前記療養者管理端末に対する療養者の応答を入力するステップと、前記療養者管理端末に設けられたセンサで前記療養者の生体情報を取得するステップと、センサ及び前記センサで取得された生体情報を前記医療従事者用端末に送信するステップとを具備してなることを特徴とする。

【0010】本発明によれば、医者、看護婦、薬剤師、栄養士等の医療従事者が入力した療養者に関する個人情報及び医療情報に基づき、前記療養者の在宅療養のための行動スケジュールを規定する動作プロトコルを生成又は修正し、療養者管理端末に動作プロトコルに基づく療養者の在宅療養のための行動スケジュールを呈示すると共に、前記療養者管理端末を介した応答や各種生体情報の計測値等を医療従事者側に送信することができるので、在宅療養者に対するきめ細かなケアが可能であり、また、検査値等の良好なコミュニケーションにより、療養者には常に適切な動作プロトコルを提供することができる。

【0011】前記医療従事者用端末から入力される医療

情報は、例えば処方に基づく投薬指示、運動指示、リハビリテーションメニュー及び生体情報計測指示の少なくとも１つを含み、前記療養者管理端末が呈示する行動スケジュールは、前記投薬指示、運動指示、リハビリテーションメニュー及び生体情報計測指示の少なくとも１つに基づく服薬指示メッセージ、運動指示メッセージ、リハビリテーション指示メッセージ及び生体情報計測指示メッセージの少なくとも１つを含む。また、本発明の一つの実施形態においては、前記医療従事者用端末は、医師用端末、看護婦用端末、薬剤師用端末及び栄養士用端末を含み、前記動作プロトコル生成手段は、前記医療従事者用端末から入力された医療情報に基づき生成される行動スケジュールに不整合が生じたときに、これを前記医療従事者に報知して修正を促すものである。

【００１２】また、前記動作プロトコル生成手段は、例えば前記療養者管理端末からの療養者の応答に基づいて前記動作プロトコルを適宜修正したり、療養者の行動を行動検出手段で検出し、前記行動検出手段による前記療養者の行動の検出結果に基づいて前記動作プロトコルを適宜修正するものである。これにより、療養者の行動状況や体調等に応じた柔軟な行動スケジュールを生成することができる。

【００１３】また、療養者の特定の生体情報の真値又は真値として扱われているデータと、前記療養者管理端末での計測結果とが一致するような前記療養者管理端末のパラメータを計算する手段と、このパラメータを前記療養者管理端末に設定する手段とを更に具備するようにしても良い。

【００１４】

【発明の実施の形態】以下、本発明の実施形態を図面に基づいて説明する。図１は、本発明の一実施形態に係る在宅療養者支援システムの全体構成例を示すブロック図である。このシステムは、管理者（サービス事業者）側に設けられた管理者用サーバ１０１と、療養者宅に設けられた療養者管理端末１０２と、医療機関に設けられた医療従事者用端末、即ち、医師用端末１０４、看護婦用端末１０５、薬剤師用端末１０６、及び栄養士用端末１０７とが、公衆回線（あるいはＷＡＮ）１００にて接続されて構成される。

【００１５】療養者管理端末１０２は、療養者との対話機能、療養者の生体情報の取得機能及び医療機関への情報伝送機能を有するもので、所定の動作プロトコルに従って所定の処理を実行するＣＰＵ１０２１と、各種データ及びアプリケーションプログラムを記憶するメモリ１０２２及びハードディスクドライブ（ＨＤＤ）１０２３と、管理者用サーバ１０１及び医療従事者用端末１０４～１０７との間で通信を行うための通信部１０２４とを備える。図２は、療養者管理端末１０２の外観を示す。端末本体１０２０には、療養者とのマンマシンインタフェースを構成する表示部１０２５、タッチパネル１０２６、音声発生部１０２７、音声入力部１０２８、振動発生部１０２９及びＣＣＤカメラ１０３０が搭載されている。

【００１６】また、療養者管理端末１０２は、各種の生体情報検出用のセンサ１０３１～０１３６を備える。即ち、端末１０２には、腕に巻き付ける腕輪センサ２０１が備えられ、この腕輪センサ２０１には、血糖値センサ１０３１、光電脈波センサ１０３２及び血中飽和酸素濃度（ＳｐＯ２）センサ１０３３を一体化した光電センサ２０２と、血圧センサ１０３４とが内蔵されている。このようなセンサは、特に糖尿病の患者向けには有効である。また、鼓膜式体温計１０３５及び心電計（心電電極）１０３６が端末本体１０２０にオンラインで接続されている。ここで血糖値センサ１０３１としては、光学的に血中のグルコース濃度を計測できるタイプのセンサを用いる。また、血圧センサ１０３４としては、通常タイプの他、脈波伝播時間から計測する光学式の血圧センサを用いてもよい。その場合、血圧センサ１０３４は、血糖値センサ１０３１、光電脈波センサ１０３２、及び血中飽和酸素濃度センサ１０３３などと一体化した光電センサ２０２とすることができる。脈波伝播時間を計測するためには、心電図による心拍と脈波のピークの時間差を計測する。

【００１７】管理者用サーバ１０１には、管理者用端末１０１１とプロトコルデータベース（ＤＢ）１０１２とが設置される。プロトコルデータベース１０１２には、療養者管理端末動作プロトコルのデータが登録される。療養者管理端末動作プロトコルとは、療養者管理端末１０２が行う、療養者に対する服薬時間や生活行動の指示、データ計測の指示などを行う音声メッセージあるいは画面表示の出力のタイミングおよび内容、さらに端末１０２の内部での処理内容を記述するものである。これらは端末１０２上で動作するアプリケーション内に固定で設定されるものでなく、テキストデータとして管理されるため、内容変更に伴うアプリケーション自体の差し替えや再コンパイルは不要で、テキストデータのスクリプトを修正、あるいは差し替えするだけでアップデートが可能である。

【００１８】図３は、上記の療養者管理端末動作プロトコルの一例を示したものである。ここでは第一の実施例としてスケジュール固定の場合を示している。図３に示すように、プロトコルは端末１０２の動作のスケジュールを管理し、この時刻やイベントに従って端末１０２が動作する。

【００１９】また、プロトコルデータベース１０１２には、療養者の基本情報として、療養者をキーとして関連付けられた各療養者の過去の病状、病歴、身体状況（障害部位、程度など）、性格、処置歴、各バイタルサインデータの履歴、その他検査データ履歴などの医療データと、投薬の処方歴、それに対応した生活指導（運動、食

事、嗜好など）の履歴、療養者管理端末１０２での計測処方（指示）、および療養者管理端末１０２の各センサ１０３１～１０３６にて計測された生体情報が蓄積される。

【００２０】以下にシステム運用の手順を示す。全体の流れは、図４に示すように、データ登録（Ｓ１）、プロトコル生成（Ｓ２）、療養者管理端末１０２の動作開始（データ計測,キャリブレーション、データ転送）（Ｓ３）、計測データ処理・評価（医師による診察、達成度評価）（Ｓ４）、プロトコル修正（Ｓ１，Ｓ２）の流れとなり、これらの処理を繰り返す。

【００２１】在宅療養を始める際、初めに医師は療養者の基本情報、診療データ、処方データ、生活指導データを診療時などに医師用端末１０４に入力する。他の職種（薬剤師、栄養士、理学療法士など）も同様にそれぞれの処方データ、生活指導、栄養指導データをそれぞれの機関にある端末１０５，１０６，１０７から入力する。図５はこの中で特に内科医、眼科医の処方データと、栄養士による食事療法、理学療法士によるリハビリ処方のデータの例を示す。これらと、入力された上記のような療養者のデータと、管理者用サーバ１０１のメンテナンス情報を合わせて、プロトコルを生成する。生成されるプロトコルの一部は図５のように生成される。このように各職種の処方をひとつの時間軸で順番に実行するプロトコルとして生成される。プロトコルは、登録された療養者のデータをもとにシステム側が直接生成するか、管理者側で代行して作成するか、過去の類似データを検索し、これらから医師が選択、取得して、これをベースに作成してもよい。

【００２２】システムが直接作成する場合は図６のような流れとなる。入力された療養者の各データを条件に（Ｓ１１，Ｓ１２，Ｓ１３）、管理者用サーバ１０１があらかじめ管理者用端末１０１１内に持っている判定ロジックに従い、プロトコルを生成する（Ｓ１４）。作成されたプロトコルは、プロトコルデータベース１０１２に登録する（Ｓ１５）と共に療養者管理端末１０２へ送信され、端末１０２上に登録される（Ｓ１６）。その際、療養者の各基本情報に従い、障害により指示するメディアを変更し療養者にあった呈示方法（視覚障害者であれば音声対話にする、など）にし、また性格により指示方法（回数、タイミング：うるさく言われるのを嫌うタイプの人には回数を少なくする、あるいは画面指示のみにする、など）を変更する。そのプロトコルデータに従い端末１０２は動作する（Ｓ１７）。端末１０２は、療養者にデータを計測する指示を行い（Ｓ１８）、データを収集し（Ｓ１９）、収集したデータを管理者用サーバ１０１に転送する（Ｓ２０）。管理者用端末１０１１は、転送されたデータをプロトコルデータベース１０１２に登録する（Ｓ２１）とともに、医師に特徴的なデータを抽出し、診察用データとして医師用端末１０４に送信し（Ｓ２２）、医師による診断を依頼する（Ｓ２３）、医師は処方や生活指導などのデータを修正し再度管理者用サーバ１０１に転送する（Ｓ２４）。管理者用サーバ１０１は、ここで転送された修正データに基づきプロトコルを修正し（Ｓ２５）、これを療養者管理端末１０２に送信すると共にプロトコルデータベース１０１２に追加登録する（Ｓ２６）。療養者管理端末１０２では、修正されたプロトコルを登録し（Ｓ２７）、修正されたプロトコルに基づき動作を再開する（Ｓ２８）。このような流れを繰り返すこととなる。

【００２３】類似データよりプロトコル生成を行う場合は、図７のような流れとなる。入力された各データが管理者用サーバ１０１のプロトコルデータベース１０１２に転送され、これに基づき、プロトコルデータベース１０１２のなかから管理者用端末１０１１のＣＰＵが療養者の類似状況データを検索する（Ｓ３１）。検索された類似状況のデータセットは医師、および看護婦用端末に送信され（Ｓ３２）、医師、看護婦はこのデータに従い、類似状況での処方、生活指導などを参考に作成したデータを修正する（Ｓ３３）。また食事指導として栄養士が食事、運動メニューを作成し、これをそれぞれの端末から入力する（Ｓ３４）。この場合も医師と同様、療養者の情報をプロトコルデータベース１０１２に送り、類似状況データを検索、取得し（Ｓ３５）、これに基づいてメニューを作成する（Ｓ３６）。医師、看護婦、薬剤師、栄養士など医療従事者により、上記のように作成されたプロトコルは、作成された端末１０４～１０７から管理者用サーバ１０１に転送され（Ｓ３７）、ここから療養者管理端末１０２へ送信され、端末１０２上に登録される（Ｓ１６）。以下の流れは、図６のＳ１７～Ｓ２８と同じであるため、重複する処理の説明は割愛する。

【００２４】また図５のように複数の医療従事者が一人の患者に対して様々な処方を出している場合、これらが競合する場合も考えられる。例えば食後３０分後に血糖値計測と投薬とリハビリが重なる場合があったとき、管理用サーバ１０１が動作プロトコルを作成する際に、これらを調整するため、それぞれの処方を出した医療従事者に対して管理用サーバ１０１が電子メールで問い合わせを行い、結果を電子メールの回答で受けて、これを元に動作プロトコルの順番を決定する。例えば上記の場合では、内科医と理学療法士に「食後３０分後に血糖値計測と投薬とリハビリの処方が重なっていますがどのような手順で行いますか？　順番を回答ください。」とメールを送信する。これを受けた担当同士で相談し結果として「１：血糖値計測　２：投薬　３：投薬後３０分後にリハビリ」を管理者用サーバ１０１に送信すると、これを管理者用サーバ１０１が解釈し、動作プロトコルに設定する。このときの回答は予めフォーマットを決めておいて、このフォーマットに従って回答することで管理者

用サーバ１０１が解釈できるようにしている。

【００２５】上記の実施例の場合、療養者管理端末１０２はプロトコルに設定された時間通りに動作するが、別の実施例として、音声対話にてユーザの状況を確認しながらプロトコルの時間を調整する場合もある。その場合のプロトコル例を図８に示す。この場合は、音声対話で確認されたユーザイベントと、プロトコル内にスケジューリングされたイベントとを比較し、一致したら次のステップへ進む流れとなる。ここでは予定したイベントが遅れた場合、そのイベントに依存した以降のイベントが時間をシフトする。具体的には管理者用サーバ１０１に設定テーブルを設け、依存関係はその設定テーブルに設定する。

【００２６】さらに別の実施例として、療養者の状況をウェアラブルセンサ、もしくは周囲に設置した環境側のセンサを用いて認識し、得られた状況に合わせて療養者管理端末１０２を動作させるようにしても良い。本実施例の構成を図９に、この場合のプロトコル例を図１０に示す。図９において、療養者管理端末１０２は、図１に示したものと同一構成である。ウェアラブル・センサ５０１は、ベルト、腕輪、ヘッドギヤ等の形態で療養者の身につけて、療養者の状態をモニタするためのもので、腰部加速度センサ５０１１、顎部加速度センサ５０１２、脈波センサ５０１３、音声入力部５０１４、ＣＣＤカメラ５０１５、振動発生部５０１６等の各種の状態検出センサを有する。また、ワイヤレスで計測データを療養者管理端末１０２に送信するため、内部にＣＰＵ５０１７、メモリ５０１８及び無線の通信モジュール５０１９を内蔵している。

【００２７】療養者がウェアラブルセンサ５０１として加速度センサを腰部（５０１１）および顎部（５０１２）に装着し、これにより療養者の動作を認識し、療養者の動作とスケジュールとから療養者の行動を認識する。このような認識処理は,例えば特願２０００-０６９８２３に開示されている,本実施例では,特願２０００-０６９８２３と同様に加速度センサ５０１１を腰につけて動作と姿勢を認識し、さらに顎にも加速度センサ５０１２をつけて、顎が断続的に動く場合、食事中あるいは会話中であると認識する。食事中か会話中かは顎の動きに同期して発声しているかを音声入力部（マイクロフォン）５０１４で計測することで行う。また筋電計測用の電極を咀嚼筋上に装着し、あごの動きによる筋電から動き（咀嚼の強さ、回数）を計測し、食事中であるかどうかを認識しても良い。

【００２８】本実施例では、図１０に示すように、定時のプロトコルだけでなく、認識された状況をイベントとしてそれぞれに対応したプロトコルが定時のプロトコルに割り込んで動作し、予定のプロトコルは状況に合わせて変更される。ただし、イベント間の関係もあり、たとえば、運動指導として「午前中に散歩３０分」と指示されていた場合、プロトコルとしては、上記のような食事中認識方法により朝食を認識した場合、その後１時間後ぐらいに「３０分程度散歩してみましょう？」とメッセージを出すが、その前にすでに散歩している場合（すなわち動作「歩行」が継続している場合）はメッセージ表示を行わない。

【００２９】図６のように、システムによりプロトコル修正を行う場合は、プロトコルに沿って実施された結果（実績）を評価し、達成度を求め、達成度を高めるようにプロトコルを修正する。達成度とは与えられた指示、指導のメニューの実施割合として求める。ここでは動作プロトコル作成前に入力された各担当（医師、看護婦、薬剤師、栄養士）の処方を示す。以下にその手順を示す。

【００３０】まず、実績データを取得する。取得方法としては、上記の３つの実施例のうち、１番目（プロトコルが固定の場合）のと２番目（対話によりプロトコルをシフトする場合）の場合、プロトコルに組み込んだ音声対話、画面入力により取得する。３番目（ウェアラブルセンサにより状況認識する場合）の実施例の場合、ウェアラブルセンサ／環境センサにより実績データを取得する。

【００３１】音声対話、画面入力の場合では、運動情報の取得については、たとえば散歩の予定時間になると散歩をしているかどうか確認し、散歩している、あるいは散歩し終わったという回答が得られたときにその負荷状況、時間を確認して実績として記録していく。１番目の場合、これによりプロトコルの時間を調整することはないが、２番目ではこれに伴い以降のプロトコルをシフトしていく。

【００３２】また食事情報の取得については、画面の対話形式で食事内容を入力し、これらも実績データとする。食事内容の入力画面の例としては、図１１、あるいは図１２のような画面で入力する。図１１では、食事のメニューを選択すると、療養者管理端末１０２上に持つテーブルによりメニューと各栄養分との対応関係を取得し、それぞれの栄養分ごとの摂取量を換算し、カロリーを計算する。図１２では、各栄養分を療養者が直接画面上のバースライダーを用いて入力する。

【００３３】３番目のセンサを用いた場合では、運動情報に関しては、散歩であれば継続歩行の時間と、加速度センサ５０１１，５０１２の振幅、あるいは脈波センサ５０１３から得られる心拍数から運動負荷を求め、運動量を求め実績データとする。また、食事情報に関しては、上記のようなマイクロホン、加速度センサなどを用いて食事状況を認識し、食事内容に関しては対話にて取得するか、画像から取得する。これらを一日、あるいはメニューごとに集計し、その達成度を計算する。達成度を評価し、達成度の低いメニューについては、メッセージの出し方を変更し、その効果を随時確認しメッセージ

の出し方を変更していく。たとえば運動量の実績が想定より少なかった場合、運動履歴を確認し、メッセージを出しても運動が行われなかった場合（たとえば「（午前中に）１時間ほど散歩しましょう」に対して、午前中に連続歩行にならなかった場合）、メッセージをさらに厳しい表現、あるいはメッセージ発生頻度を増加させるようなプロトコル変更を行う。これらの変更のルールはテーブル化してサーバ内に持ち、ユーザの性格や過去の実績から効果的なパターンを選択する。また全体的に達成率が悪い場合、指示方法を見直す。たとえば画面指示でよくない場合、音声対話に切り替え、効果を比較し良い方を採用する。

【００３４】療養者管理プロトコルの修正時は、作成時と同様に、処方された生体情報計測時間（例：個々の食事時間に合わせて食後の時間で設定する）、患者の身体障害状況（例：失明患者であれば音声合成、認識のみ）、性格（例：うるさく言ったほうが効くタイプならメッセージを多くする）とシステム管理スケジュール（キャリブレーション等）をあわせてスケジューリングしてプロトコルを修正する。プロトコルを達成度に沿って、これを改善するために修正する際、上記のような療養者ごとの状況に合わせて修正する方向性を決める。

【００３５】また療養者管理端末にて使用するセンサのうち、血糖センサ、光学式血圧センサなどキャリブレーションが必要なものについて、キャリブレーション条件（時刻、内容）など療養者管理端末のメンテナンス情報を管理者がプロトコルデータベースへ登録しておく。たとえば、血糖センサは、採血して得られた血糖値を元に同時に得られたセンサ出力の値からパラメータを校正するようなキャリブレーションが必要となる。

【００３６】療養者管理端末１０２のキャリブレーションのスケジュールは療養者管理端末の動作プロトコルに含まれる場合もある。図１３に示すように、該当する日の朝に病院へ行き、直接検査を受けるように指示するメッセージを表示する（Ｓ４１）ような処理がプロトコルに含まれる。病院では採血により血糖値など詳細データを取得し（Ｓ４２）、これと同時にキャリブレーション用に取得した療養者管理端末の計測データセット（血糖値計測のための元データ）をもとに療養者管理端末の出力データ（血糖値）と採血で得られたデータ（血糖値の真値として扱う）が一致するように、パラメータの調整を行う（Ｓ４３）。調整された新しいパラメータは、ネットワークを介して療養者宅の療養者管理端末に転送され、自動的に設定される。もしくはパラメータをフロッピー（登録商標）ディスク、メモリーカードなどのメディアに転送し、療養者がこれを自宅に持ち帰り、療養者宅の療養者管理端末のスロットに挿入し、パラメータ設定アプリケーションを起動し設定してもよい（Ｓ４４）。

【００３７】ここではキャリブレーション用の計測データは通院時のものだけを用いたが、例えば過去３日間の計測データをキャリブレーション予定日にシステムが自動的にメディアに保存し、これを療養者が病院に持参してもよい。また、キャリブレーションを予めスケジュールを固定するのでなく、療養者の通院時に行う場合もある。療養者は通院時に採血により血糖値を計測され、そのデータは医師側端末１０４に入力される。そのときにシステムがネットワークを介して療養者宅の療養者管理端末１０２から最新の計測データセット（血糖値計測のための元データ）を受信し、このデータをもとに採血のデータと端末による推定値が一致するように新しいパラメータを求め、これを上記と同様にネットワークかメディアを介して療養者宅の端末に設定する。あるいは、療養者は通院時に直前の非侵襲の計測データセットを保存したメディアを持参する。採血データが医師側端末から入力されたときに持参したメディアのデータを用いて新しいパラメータを求め、これをメディアに新たに保存する。このメディアを療養者宅の端末のメディア読み書き用のスロット（図示しない）に差し込むと療養者管理端末が新しいパラメータを認識し、これを自動的に療養者管理端末に設定する。

【００３８】もしくは、図１４に示すように療養者が自分でキャリブレーションを行う場合もある。キャリブレーションが必要な日時に、端末から採血による自己血糖計測が可能なセンサを用いて採血で血糖値を計測するように指示する（Ｓ５１）。計測が終わり血糖値を端末に入力させる（Ｓ５２）。次に通常の非採血による計測を行わせて、出力データを取得する（Ｓ５３）。得られた出力データと、採血にて計測した血糖値が一致するようにパラメータを調整する（Ｓ５４，Ｓ５５）。また時間を置いて複数回のデータを用いて精度を向上させる必要があるため、このような採血とパラメータ調整の作業を決められた時間に数回行うようにプロトコルに記述される。

【００３９】また、図１５に示すように、訪問看護婦が訪問時にキャリブレーション操作を行う場合もある。訪問時に看護婦が採血による血糖計測を行い（Ｓ６１）、その結果を端末１０２に入力する（Ｓ６２）、同時に非採血の血糖計測も行い（Ｓ６３）、そのデータと採血によるデータとが結果が一致するように端末内でパラメータを計算し（Ｓ６４）、新しいパラメータを設定する（Ｓ６５）。もしくは、図１６に示すように療養者宅でデータ収集を行い、データを管理者用サーバ１０１に転送し（Ｓ７１）、サーバ１０１にて新しいパラメータを求めて（Ｓ７２）、これを療養者管理端末１０２に送り返して（Ｓ７３）、設定する場合もある（Ｓ７４）。

【００４０】また上記のようなキャリブレーション処理を管理者用サーバ１０１にて行う場合もある。キャリブレーションの必要な日時等の情報を管理者用サーバ１０１が持ち、このスケジュールに基づいて、その直近に計

測された療養者管理端末１０２の計測データセット（血糖値計測のための元データ）、および採血による血糖値データを収集し管理者用サーバ１０２に蓄積する。このデータを用いて療養者管理端末１０２による計測結果が採血による血糖値と一致するようにパラメータを修正する。修正したパラメータはネットワークを介して療養者宅の端末に設定される。ここで医師、看護婦等に採血による血糖値の計測を促すメッセージ配信と、療養者宅に療養者管理端末にて血糖値を計測するようなメッセージ配信を行ってもよい。

【００４１】また、別の実施例として、作成されたプロトコルに含まれる薬品や食品を、それぞれの宅配業者に発注して宅配により投薬や食事の管理を行う例について説明する。その場合の構成図を図１７に示す。また、宅配業者との関連のフローチャートを図１８に示す。病院にてプロトコルが完成し、療養者管理端末１０２へ送信処理を行う際、送信データの中に含まれる投薬情報を抽出し（Ｓ８１）、これを提携する薬品宅配業者１１０へ送信する（Ｓ８２）。また、食事指導データ又は食事メニューを抽出し（Ｓ８１）、これを食品業者に送信する。それぞれの業者は受信データに従い療養者宅へ薬品、食品を宅配する（Ｓ８４，Ｓ８５）。食品業者の場合、受信するデータが食事指導データだけである場合もあり、このときは食事の具体的なメニューを作成し（Ｓ８３）、療養者に事前に承認を得るためメニューを送信しておく（Ｓ８６，Ｓ８７）。

【００４２】また、以下の実施例では、プロトコル内に関連業者の広告を織り交ぜ、療養者管理端末１０２の画面上にバナー広告として表示し、療養者、およびその家族が関連商品のオンラインショッピングができるようにする。ここで作成するプロトコルには、関連商品のバナー広告のためのリンク情報とバナーデータを図１９のように組み込む。このプロトコルを受信すると、端末ではそれぞれの時間に合わせて図１１のようにバナー広告表示を行う。ユーザがこれをタッチパネルで選択すると、療養者管理端末１０２は、インターネット上のリンクページにアクセスし、療養者管理端末１０２上でＷｅｂブラウザを表示し、オンラインショッピングなど関連業者のサイトを利用することを可能とする。また管理者は広告を療養者管理端末１０２上に表示することで、この関連業者よりバナー広告料を徴収する。

【００４３】なお、以上の実施例で示した動作プロトコルは、たとえばＸＭＬを使ったマルチメディア同期再生言語ＳＭＩＬの書式にならって図２０のように記述する。ここでは、ひとつのメッセージ表示の場面のみを記述している。２００１年４月１日の１０：００に複数の画像と音声とテキスト１５秒間、２シーン表示する例を示している。表示だけでなく入力がある場合ＪａｖａＳｃｒｉｐｔなどで記述し、Ｗｅｂブラウザで動作させることも可能である。

【００４４】なお、上記実施例では、管理者用サーバ１０１は医療機関と独立に設置しているが、これは医療機関がこの業務を兼ねて管理者用サーバ１０１を医療機関内に設置しても、その他の処理は同様である。また医療従事者用端末にこれが含まれてもよい。また、その他ここで示した実施例はあくまで一例で、この構成の限りでない。

【００４５】このように、本実施形態の在宅療養者支援システム及び方法によれば、プロトコルデータベースに基づき在宅療養者支援端末を制御する動作プロトコルを、療養者の障害、性格などに合わせてきめ細かく生成することで、医師など医療従事者の負担を低減しつつ、きめ細かい生活指導やデータ収集が可能で、さらにメンテナンスの自動化が可能となる。療養者にとっても様々な医療従事者からの処方それぞれを意識して自ら管理しなくても療養者管理端末で一元管理されるため、スムーズで確実なサービスを受けることができる。さらにこれらのサービスを行うビジネスをオンラインショッピングや食事薬品宅配サービスと連携することで実現できる。

【００４６】

【発明の効果】以上述べたように、本発明によれば、医療従事者が入力した療養者に関する個人情報及び医療情報に基づき、前記療養者の在宅療養のための行動スケジュールを規定する動作プロトコルを生成又は修正し、療養者管理端末に動作プロトコルに基づく療養者の在宅療養のための行動スケジュールを呈示すると共に、前記療養者管理端末を介した応答や各種生体情報の計測値等を医療従事者側に送信することができるので、在宅療養者に対するきめ細かなケアが可能であり、また、検査値等の良好なコミュニケーションにより、療養者には常に適切な動作プロトコルを提供することができる。

【図面の簡単な説明】

【図１】　本発明の実施形態に係る在宅療養者支援システムの全体構成を示すブロック図。

【図２】　同システムにおける療養者管理端末の外観を示す斜視図である。

【図３】　本発明の第１の実施例に係る動作プロトコルの内容例を示す図。

【図４】　同システムのメインフローチャートである。

【図５】　同システムにおける各医療従事者が入力する処方の例と、メンテナンススケジュールの例と、これらを統合した動作プロトコルの例を示す図である。

【図６】　同システムにおける動作プロトコルをシステムが自動生成する場合のサービスのフローチャートである。

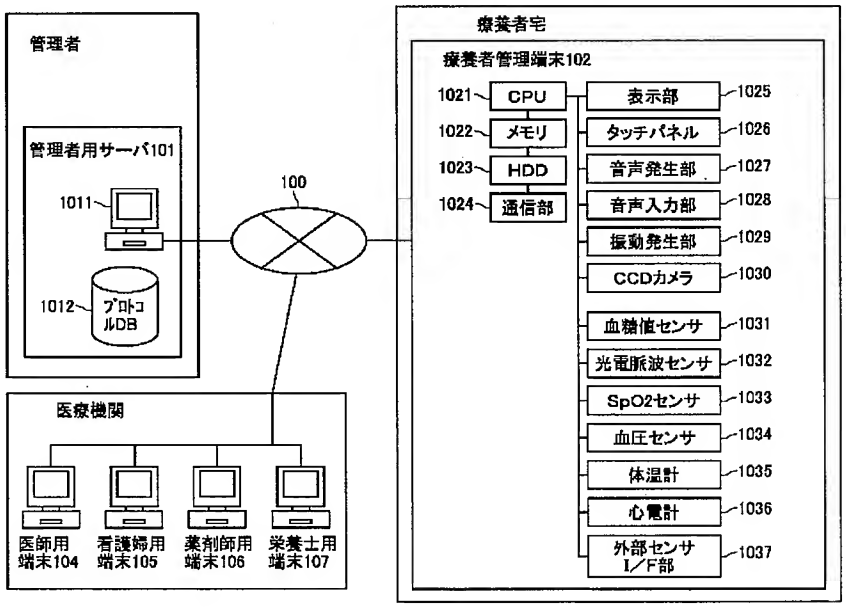
【図７】　同システムにおける動作プロトコルを医師、看護婦、薬剤師、栄養士がマニュアルで作成する場合のサービスのフローチャートである。

【図８】　本発明の第２の実施例に係る動作プロトコルの内容例を示す図である。

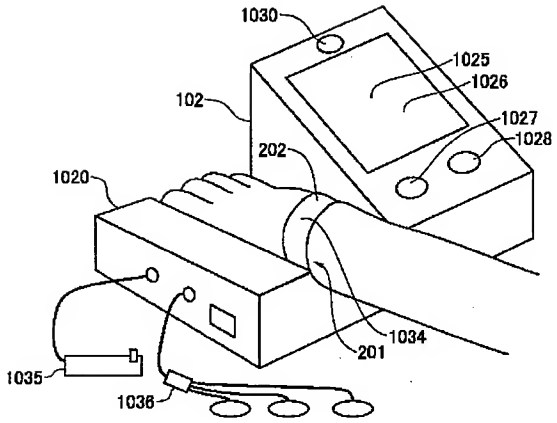
【図９】　本発明の第３の実施例に係る療養者管理端末とウェアラブルセンサの構成例を示す図である。
【図１０】　本発明の第３の実施例に係る動作プロトコルの内容例を示す図である。
【図１１】　療養者管理端末上に広告を示す場合の食事内容入力画面（例１）を示す図である。
【図１２】　療養者管理端末上に広告を示す場合の食事内容入力画面（例2）を示す図である。
【図１３】　病院でキャリブレーションを行う場合の処理のフローチャートである。
【図１４】　自宅でキャリブレーションを行う場合（パラメータを療養者管理端末内部で求める場合）の処理のフローチャートである。
【図１５】　訪問看護婦がキャリブレーションを行う場合（パラメータを療養者管理端末内部で求める場合）の処理のフローチャートである。
【図１６】　訪問看護婦がキャリブレーションを行う場合（パラメータを管理用サーバで求める場合）の処理のフローチャートである。
【図１７】　各業者間のつながりを示す関係図である。
【図１８】　薬品、食品宅配業者と連携する場合の処理の流れを示す図である。
【図１９】　療養者管理端末上に広告を示す場合の動作プロトコルの内容例を示す図である。
【図２０】　本発明における動作プロトコルの記述例を示す図（SMILを利用した場合）である。
【符号の説明】

１０１	管理者用サーバ
１０２	療養者管理端末
１０４	医師用端末
１０５	看護婦用端末
１０６	薬剤師用端末
１０７	栄養士用端末
１０１１	管理者用端末
１０１２	プロトコルデータベース
２０１	腕輪センサ
２０２	光電センサ
１０３１	血糖値センサ
１０３２	光電脈波センサ
１０３３	血中飽和酸素濃度センサ
１０３４	血圧センサ
１０３５	鼓膜式体温計
１０３６	心電電極

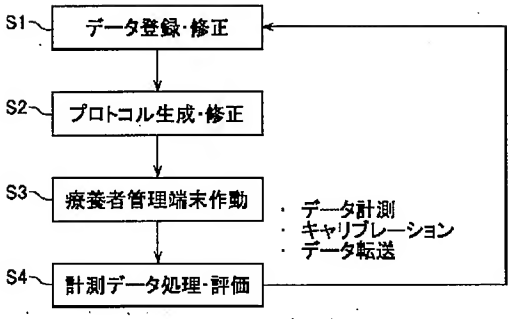
【図１】



【図2】



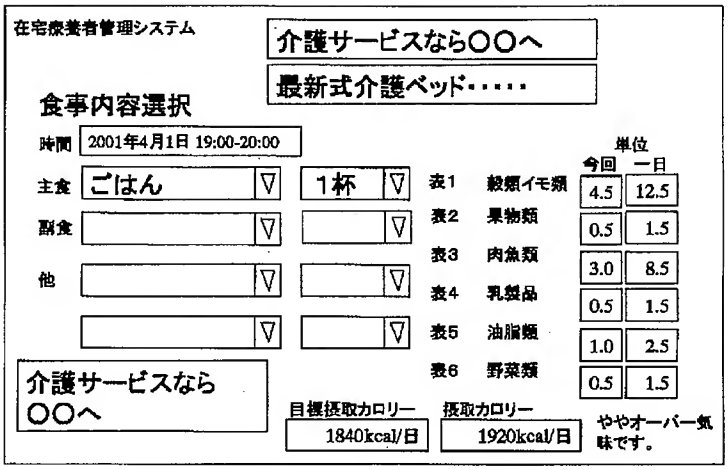
【図4】



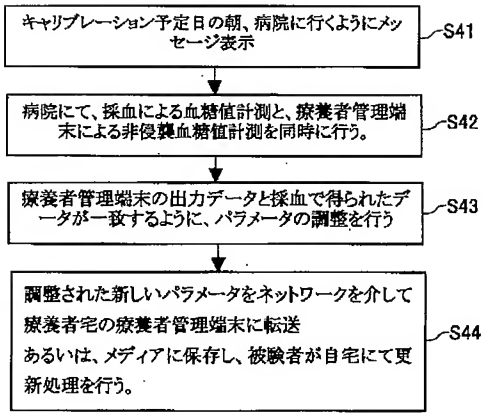
【図3】

イベント	処理	メッセージ
7:00	アラーム	
7:00	音声出力	「おはようございます。起きましょう。」
7:30	音声出力	「朝食をとりましょう。」
	音声出力	「食事内容を入力してください。」
	画像出力	食事内容を選択する画面を表示する。
8:00	音声出力	「朝食後30分以内に薬を飲みましょう。薬は画面に表示した3点です。」
8:00	画像出力	薬のパッケージ写真と数量を画面に表示する。
8:30	音声出力	「計測時間です。腕輪センサを腕に装着しましょう。」
8:31	音声出力	「準備ができたらスタートボタンを押してください。」
ボタン押下	計測処理開始	「計測を開始しました。」
終了時	計測終了、データ保存、転送	「計測を終了しました。センサをはずして結構です。」
10:00	音声出力	「運動の時間です。30分の散歩をしましょう。」

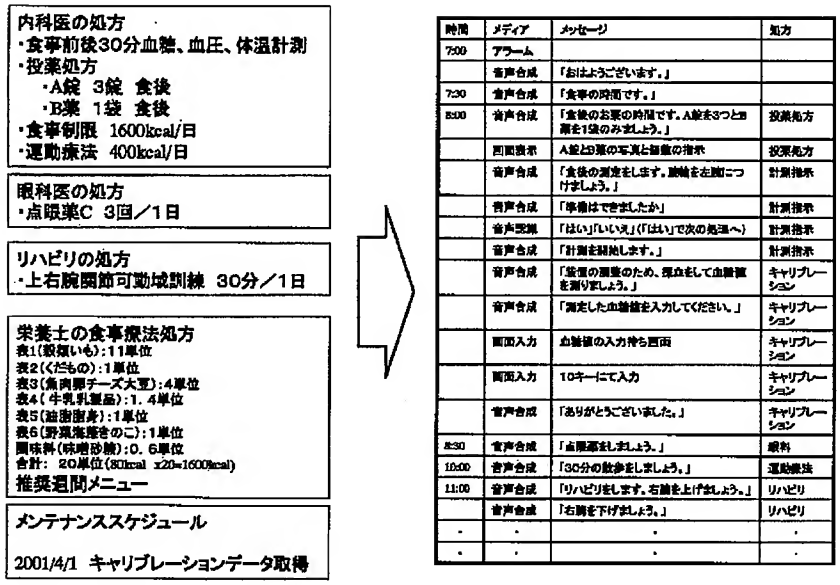
【図11】



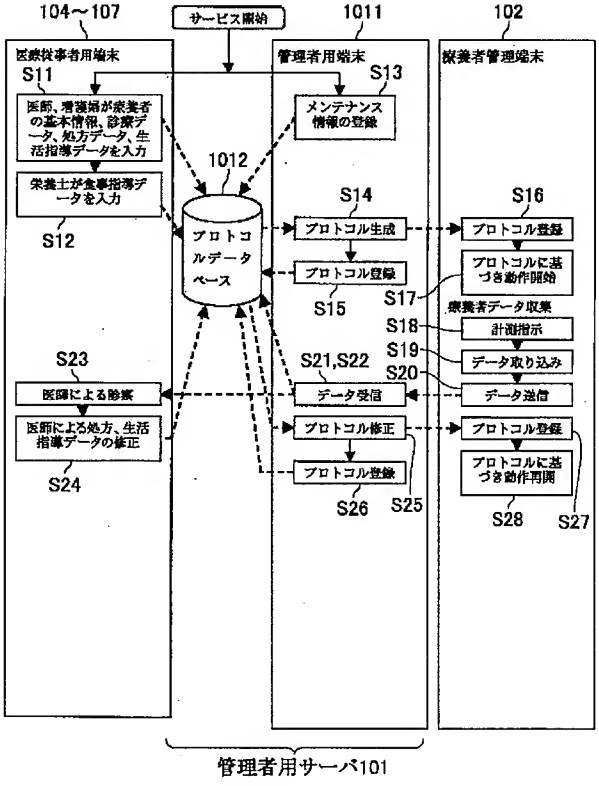
【図13】



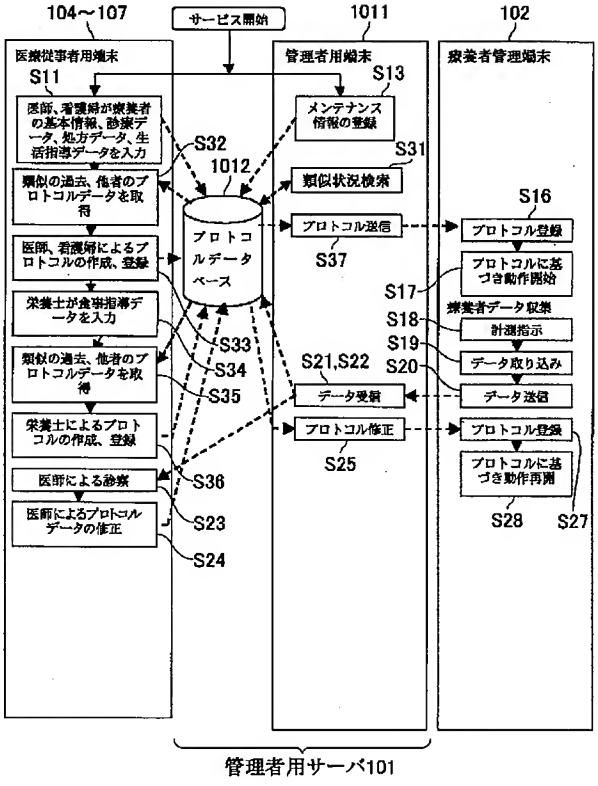
【図5】


内科医の処方
・食事前後30分血糖、血圧、体温計測
・投薬処方
・A錠 3錠 食後
・B薬 1袋 食後
・食事制限 1600kcal/日
・運動療法 400kcal/日
眼科医の処方
・点眼薬C 3回／1日
リハビリの処方
・上右腕関節可動域訓練 30分／1日
栄養士の食事療法処方
表1(穀類いも):11単位
表2(くだもの):1単位
表3(魚肉卵チーズ大豆):4単位
表4(牛乳乳製品):1.4単位
表5(油脂脂身):1単位
表6(野菜海藻きのこ):1単位
調味料(味噌砂糖):0.6単位
合計: 20単位(80kcal x20=1600kcal)
推奨質問メニュー
メンテナンススケジュール
2001/4/1 キャリブレーションデータ取得
時間 メディア メッセージ 処方
7:00 アラーム
音声合成 「おはようございます。」
7:30 音声合成 「食事の時間です。」
8:00 音声合成 「食後のお薬の時間です。A錠を3つとB薬を1袋のみましょう。」 投薬処方
画面表示 A錠とB薬の写真と個数の指示 投薬処方
音声合成 「食後の測定をします。腕輪を左腕につけましょう。」 計測指示
音声合成 「準備はできましたか」 計測指示
音声受諾 「はい」「いいえ」(「はい」で次の処理へ) 計測指示
音声合成 「計測を開始します。」 計測指示
音声合成 「血圧の測定のため、採血をして血糖値を測りましょう。」 キャリブレーション
音声合成 「測定した血糖値を入力してください。」 キャリブレーション
画面入力 血糖値の入力待ち画面 キャリブレーション
画面入力 10キーにて入力 キャリブレーション
音声合成 「ありがとうございました。」 キャリブレーション
8:30 音声合成 「血圧器をしましょう。」 採血
10:00 音声合成 「30分の散歩をしましょう。」 運動療法
11:00 音声合成 「リハビリをします。右腕を上げましょう。」 リハビリ
音声合成 「右腕を下げましょう。」 リハビリ

【図6】


104〜107
サービス開始
1011
102
医療従事者用端末
管理者用端末
療養者管理端末
S11
医師、看護婦が療養者の基本情報、診療データ、処方データ、生活指導データを入力
栄養士が食事指導データを入力
S12
S13
メンテナンス情報の登録
1012
プロトコルデータベース
S14
プロトコル生成
プロトコル登録
S15
S16
プロトコル登録
プロトコルに基づき動作開始
S17
療養者データ収集
S18
計測指示
S19
データ取り込み
S20
データ送信
S21,S22
データ受信
S23
医師による診察
医師による処方、生活指導データの修正
S24
プロトコル修正
プロトコル登録
S25
S26
プロトコルに基づき動作再開
S27
S28
管理者用サーバ101

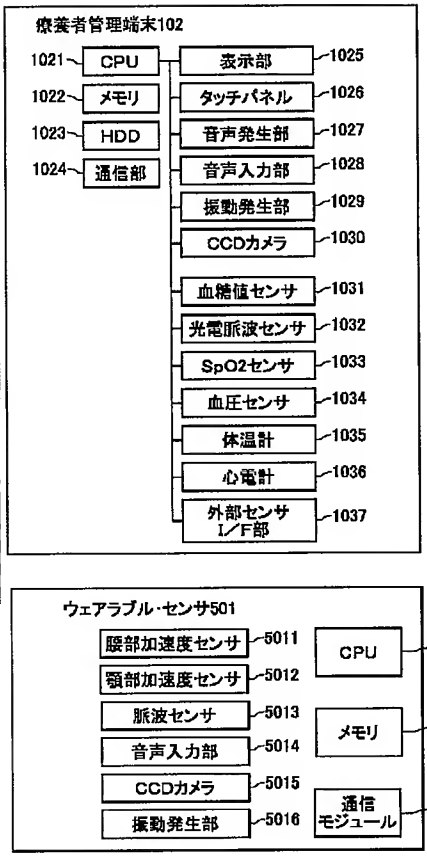
【図7】


104〜107
サービス開始
1011
102
医療従事者用端末
管理者用端末
療養者管理端末
S11
医師、看護婦が療養者の基本情報、診療データ、処方データ、生活指導データを入力
S32
類似の過去、他者のプロトコルデータを取得
医師、看護婦によるプロトコルの作成、登録
栄養士が食事指導データを入力
類似の過去、他者のプロトコルデータを取得
栄養士によるプロトコルの作成、登録
医師による診察
医師によるプロトコルデータの修正
S33
S34
S35
S36
S23
S24
S13
メンテナンス情報の登録
S31
類似状況検索
1012
プロトコルデータベース
プロトコル送信
S37
S16
プロトコル登録
プロトコルに基づき動作開始
S17
療養者データ収集
S18
計測指示
S19
データ取り込み
S20
データ送信
S21,S22
データ受信
プロトコル修正
S25
プロトコル登録
プロトコルに基づき動作再開
S28
S27
管理者用サーバ101

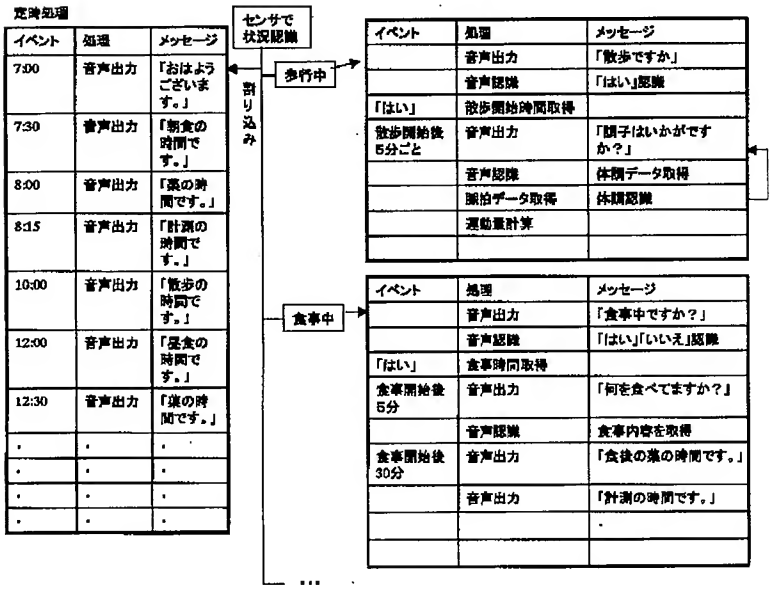
【図8】

イベント	処理	メッセージ
7:00	アラーム	
7:00	音声出力	「おはようございます。起きましょう。」
7:30	音声出力	「朝食をとりましょう。」
	音声出力	「食事中ですか？」
	音声認識	「はい」を認識
「はい」認識	音声出力	「食事内容を入力してください。」
	画像出力	食事内容を選択する画面を表示する。
8:00+食事時間のずれ	音声出力	「食後の薬を飲みましょう。薬は画面に表示した3点です。」
	画像出力	薬のパッケージ写真と数量を画面に表示する。
8:30+食事時間のずれ	音声出力	「計測時間です。脈輪センサを腕に装着しましょう。」
8:31+食事時間のずれ	音声出力	「準備ができたらスタートボタンを押してください。」
ボタン押下	計測処理開始	「計測を開始しました。」
終了時	計測終了、データ保存、転送	「計測を終了しました。センサをはずして結構です。」
10:00+食事時間のずれ	音声出力	「運動の時間です。30分の散歩をしましょう。」

【図9】



【図10】

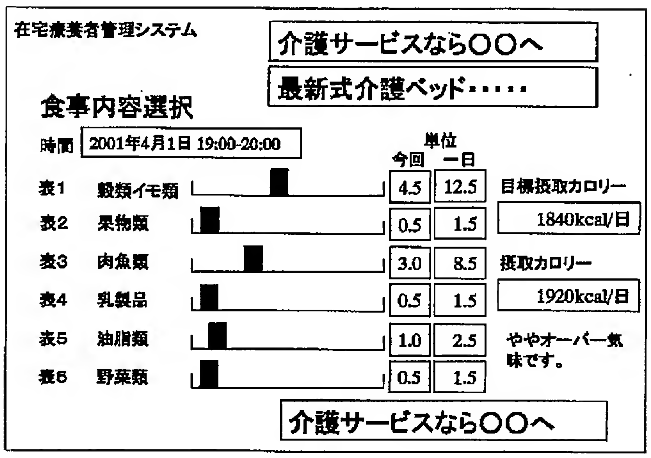


イベント	処理	メッセージ
7:00	音声出力	「おはようございます。」
7:30	音声出力	「朝食の時間です。」
8:00	音声出力	「薬の時間です。」
8:15	音声出力	「計測の時間です。」
10:00	音声出力	「散歩の時間です。」
12:00	音声出力	「昼食の時間です。」
12:30	音声出力	「薬の時間です。」
.	.	.
.	.	.
.	.	.
.	.	.

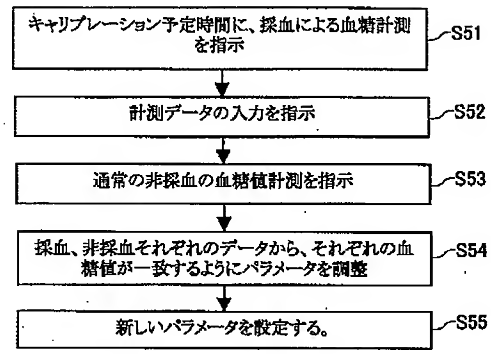
イベント	処理	メッセージ
	音声出力	「散歩ですか」
	音声認識	「はい」認識
「はい」	散歩開始時間取得	
散歩開始後5分ごと	音声出力	「調子はいかがですか？」
	音声認識	体調データ取得
	脈拍データ取得	体調認識
	運動量計算	

イベント	処理	メッセージ
	音声出力	「食事中ですか？」
	音声認識	「はい」「いいえ」認識
「はい」	食事時間取得	
食事開始後5分	音声出力	「何を食べてますか？」
	音声認識	食事内容を取得
食事開始後30分	音声出力	「食後の薬の時間です。」
	音声出力	「計測の時間です。」
		.

【図12】



【図14】



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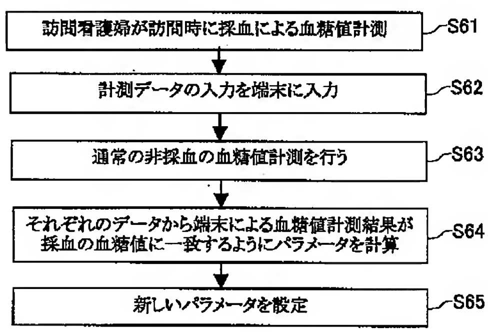
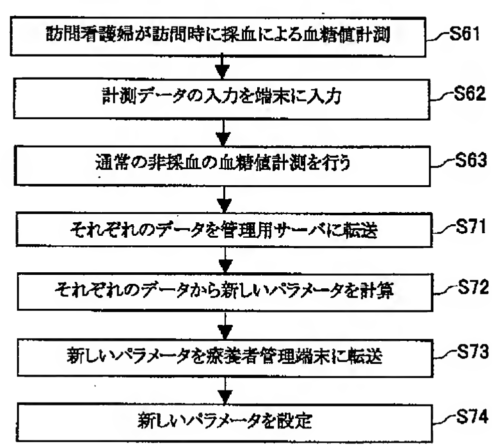


【図16】



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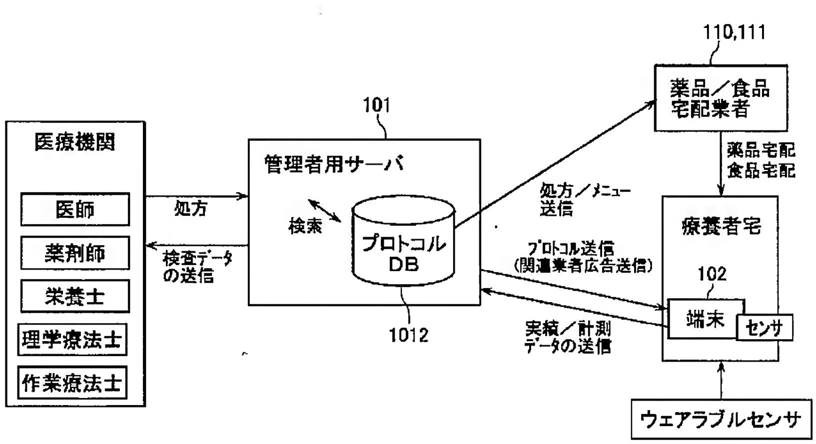

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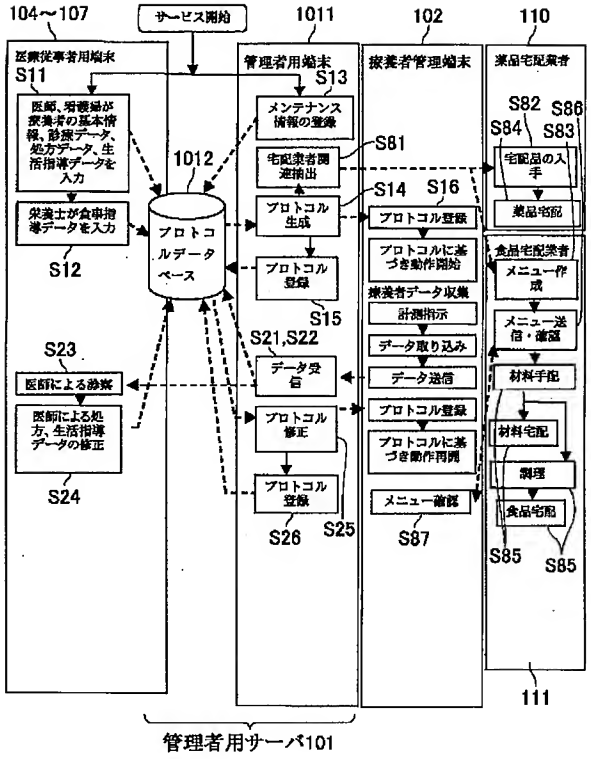

【図19】

イベント	処理	メッセージ
7:00	アラーム	(目覚まし)
7:00	音声出力	「おはようございます。起きましょう。」
7:30	音声出力	「朝食をとりましょう。」
	音声出力	「食事内容を入力してください。」
	画像出力	食事内容を選択する画面を表示する。
8:00	音声出力	「朝食後30分以内に薬を飲みましょう。薬は画面に表示した3点です。」
8:00	画像出力	薬のパッケージ写真と数量を画面に表示する。
	広告出力	「各種栄養補助食品は***薬品」
		http://www.***.*****.co.jp/
8:30	音声出力	「計測時間です。腕輪センサを腕に装着しましょう。」
	広告出力	「介護サービスなら○○へ」
		http://www.○○.****.co.jp/
8:31	音声出力	「準備ができたらスタートボタンを押してください。」
ボタン押下	計測処理開始	「計測を開始しました。」
終了時	計測終了、データ保存、転送	「計測を終了しました。センサをはずして結構です。」
10:00	音声出力	「運動の時間です。30分の散歩をしましょう。」

【図20】

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            <region id="image1" top="30" left="100" height="102" width="97"/>
            <region id="image2" top="110" left="100" height="102" width="97"/>
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    </head>
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                <img region="image2"src="http://www.***.**jp/smil/img/b.jpg"/>
                <img region="image3"src="http://www.***.**jp/smil/img/c.jpg"/>
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            </par>
            <par dur="15 s">
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                <img region="image2"src="http://www.***.**jp/smil/img/f.jpg"/>
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                <audio src= "http://www.***.**jp/smil/img/h.wav"/>
                <textstream src="text2.rt" region="text_pet" fill="freeze"/>
            </par>
        </seq>
    </body>
</smil>
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(51)Int.Cl.⁷		識別記号	FI		テーマコード(参考)
A61B	5/04		A61B	5/02	310A
	5/0402				332B
	5/11				337E
	5/145			5/04	310M
A61G	12/00			5/14	310
				5/10	310Z
					310J

Fターム(参考) 4C017 AA09 AA12 AA16 AA20 AB02
AB10 AC26 BC11 FF30
4C027 AA00 AA02 CC00 GG05 GG07
JJ01 KK03 KK05
4C038 KK01 KK10 KL05 KL07 KM00
KX01 KY04
4C341 LL30

Gateway platform for biological monitoring and delivery of therapeutic compounds

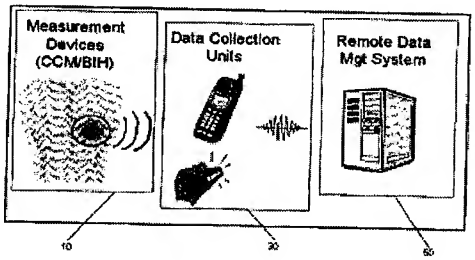
Publication number: TW552126B
Publication date: 2003-09-11
Inventor: DRINAN DARREL (US); MERZ DIETHARD (DE); EDMAN CARL (US)
Applicant: PHILOMETRON INC (US)
Classification:
- International: ***A61B5/00; G06Q50/00;*** **A61B5/00; G06Q50/00;** (IPC1-7): A61B5/00; G06F13/00
- European: A61B5/00B
Application number: TW20020114326 20020628
Priority number(s): US20010301897P 20010629; US20010032765 20011029

Also published as:
WO03049592 (A3)
WO03049592 (A2)
EP1411826 (A3)
EP1411826 (A2)
US7044911 (B2)
more >>

Report a data error here

Abstract of **TW552126B**

The invention relates to methods and devices for remote or distributed continuous monitoring of physiologically relevant states. The invention provides for methods to automatically detect deviations or other states in physiological parameters and automatically alert a measured subject, user or other authorized party. The device provides for a universal platform for sensors, and further provides for the automatic compensation or distribution of devices or bioactive agents at appropriate levels and/or intervals in response to deviations or other states sensed in various physiological parameters.



US007044911B2

(12) **United States Patent**
Drinan et al.

(10) **Patent No.: US 7,044,911 B2**
(45) **Date of Patent: May 16, 2006**

(54) **GATEWAY PLATFORM FOR BIOLOGICAL MONITORING AND DELIVERY OF THERAPEUTIC COMPOUNDS**

(75) Inventors: **Darrel Drinan**, San Diego, CA (US); **Carl F. Edman**, San Diego, CA (US); **Diethard Merz**, San Diego, CA (US)

(73) Assignee: **PhiloMetron, Inc.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 68 days.

(21) Appl. No.: **10/032,765**

(22) Filed: **Oct. 29, 2001**

(65) **Prior Publication Data**

US 2003/0004403 A1 Jan. 2, 2003

Related U.S. Application Data

(60) Provisional application No. 60/301,897, filed on Jun. 29, 2001.

(51) **Int. Cl.**
A61B 5/00 (2006.01)

(52) **U.S. Cl.** **600/300**; 128/903; 128/904; 604/174; 604/65

(58) **Field of Classification Search** 600/300–301, 600/345, 347, 361, 365; 128/903–905, 920; 705/2, 3; 604/174, 175, 290, 65–68; 607/28–32, 607/58–60
See application file for complete search history.

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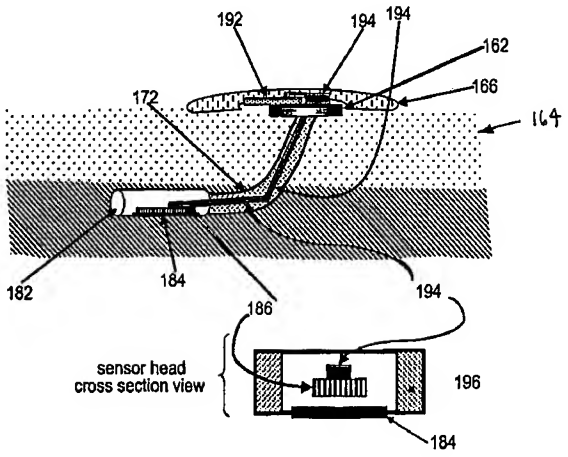
Primary Examiner—Max F. Hindenburg
Assistant Examiner—Michael C. Astorino
(74) *Attorney, Agent, or Firm*—Knobbe Martens Olson & Bear LLP

(57) **ABSTRACT**

The invention relates to methods and devices for remote or distributed continuous monitoring of physiologically relevant states. The invention provides for methods to automatically detect deviations or other states in physiological parameters and automatically alert a measured subject, user or other authorized party. The device provides for a universal platform for sensors, and further provides for the automatic compensation or distribution of devices or bioactive agents at appropriate levels and/or intervals in response to deviations or other states sensed in various physiological parameters.

12 Claims, 9 Drawing Sheets



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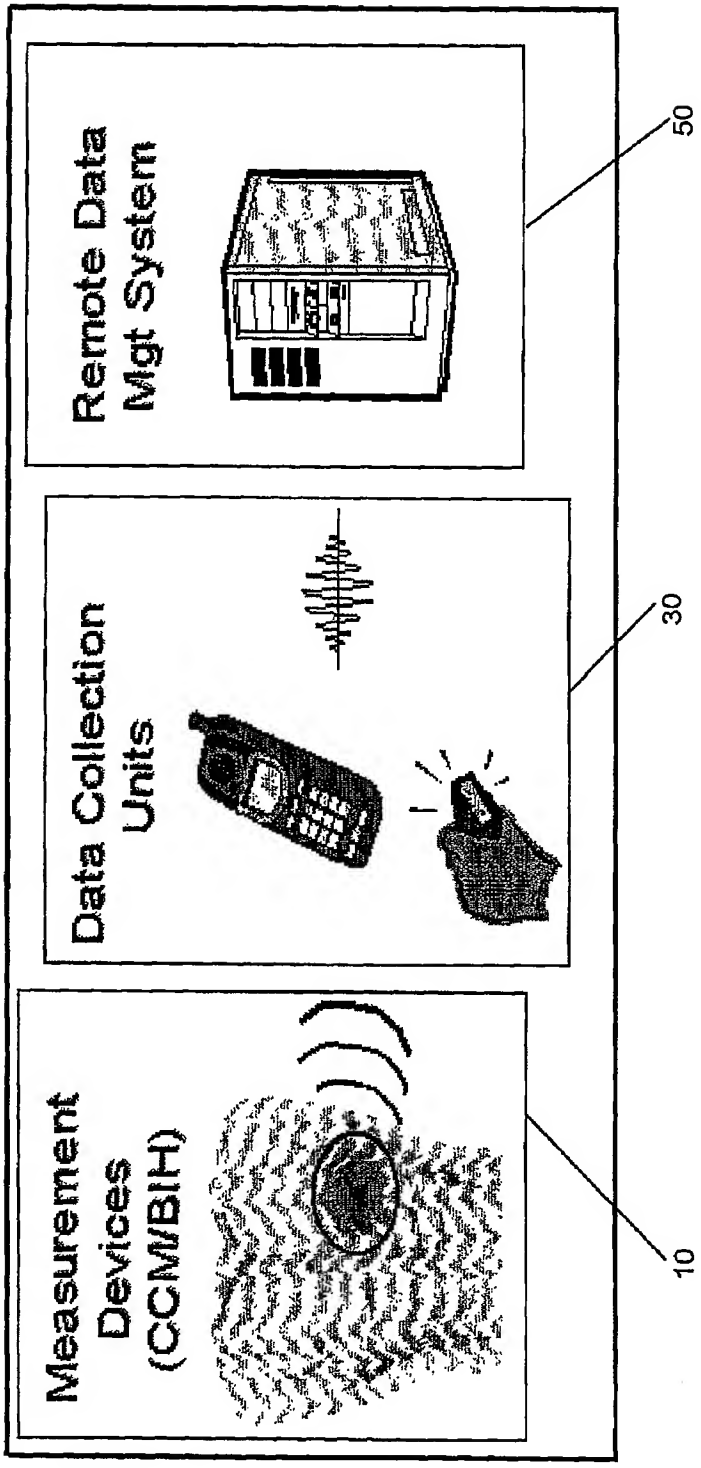
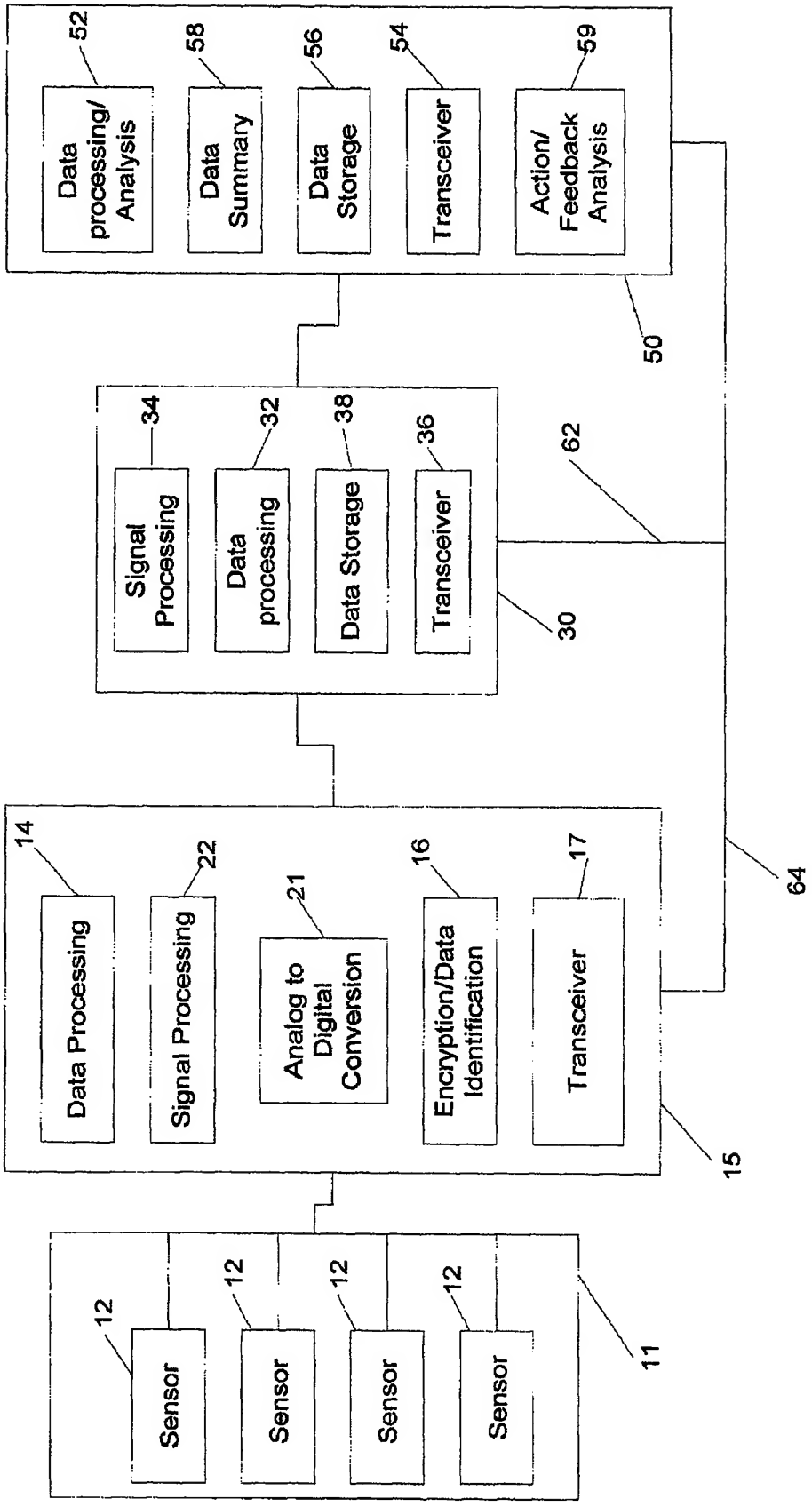

Remote Data Mgt System
50
Data Collection Units
30
Measurement Devices (CCM/BIH)
10

FIGURE 1


52
Data processing/ Analysis
58
Data Summary
56
Data Storage
54
Transceiver
59
Action/ Feedback Analysis
50
34
Signal Processing
32
Data processing
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Data Storage
36
Transceiver
62
30
14
Data Processing
22
Signal Processing
21
Analog to Digital Conversion
16
Encryption/Data Identification
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15
12
Sensor
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Sensor
12
Sensor
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Sensor
11

FIGURE 2

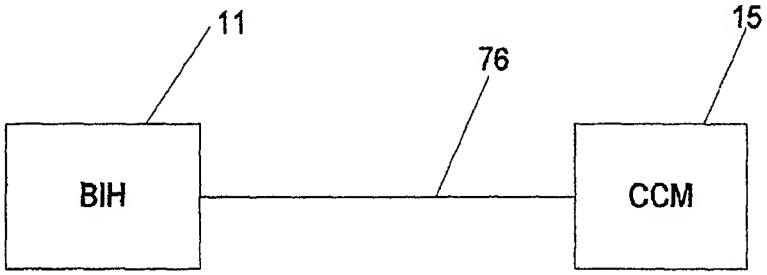

FIGURE 3

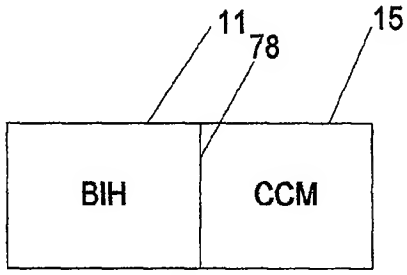

FIGURE 4

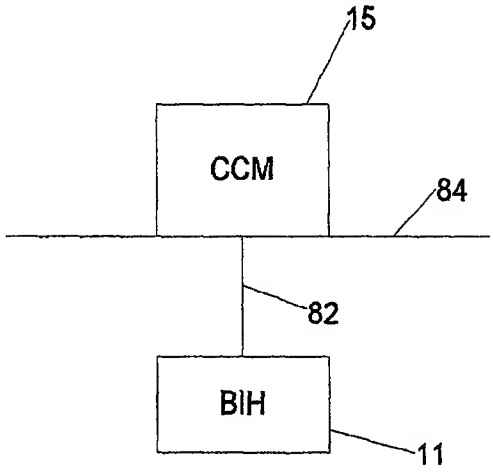

FIGURE 5

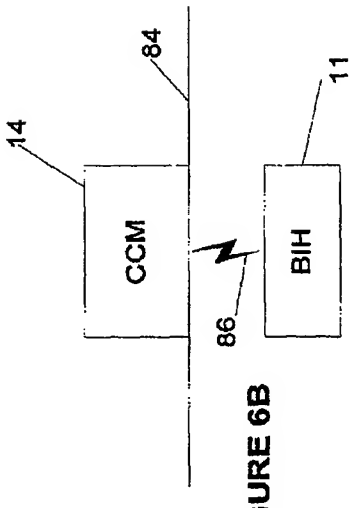

FIGURE 6B

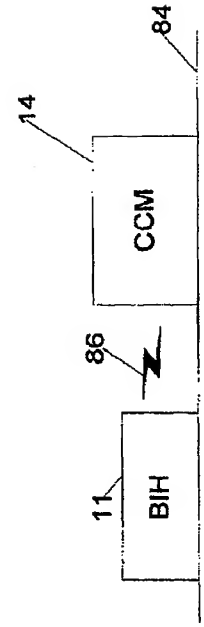

FIGURE 6A

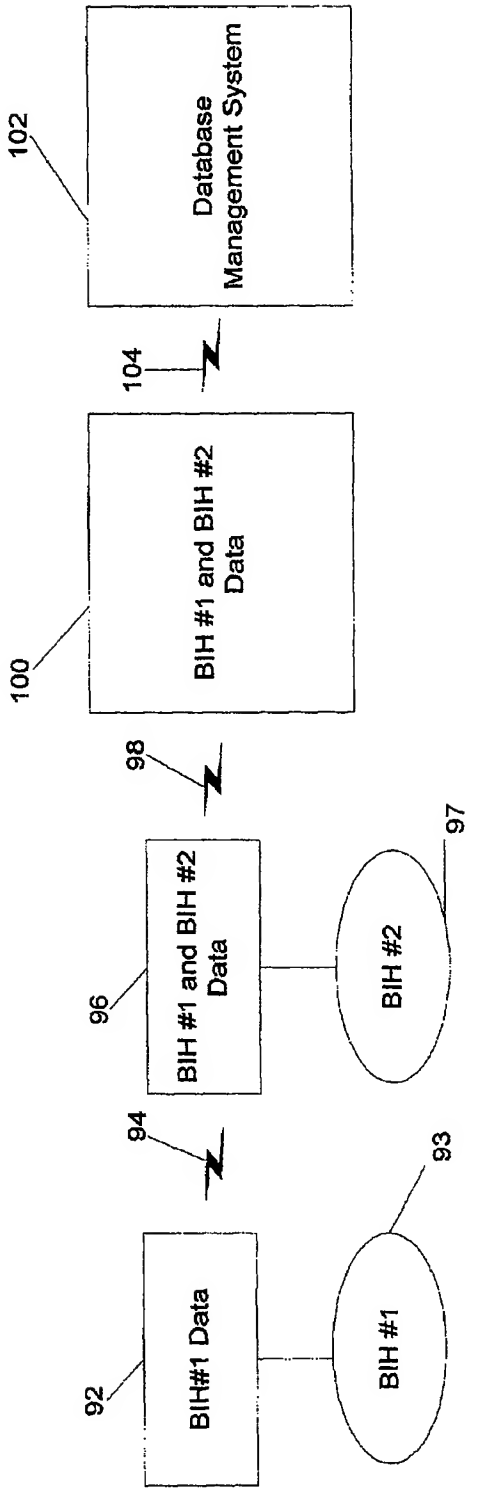

FIGURE 7

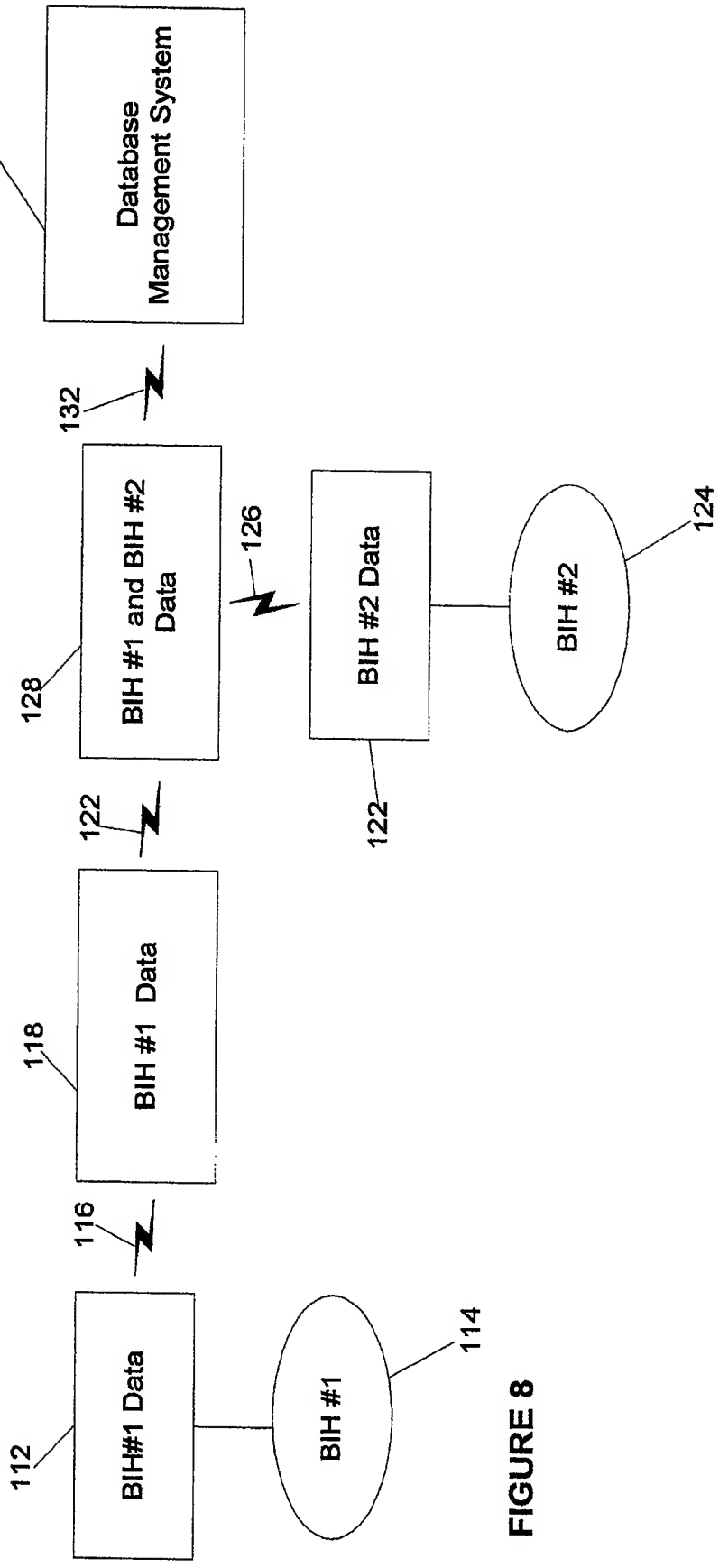
Database Management System
134
132
BIH #1 and BIH #2 Data
128
126
BIH #2 Data
BIH #2
124
122
122
BIH #1 Data
118
116
BIH#1 Data
BIH #1
114
112

FIGURE 8

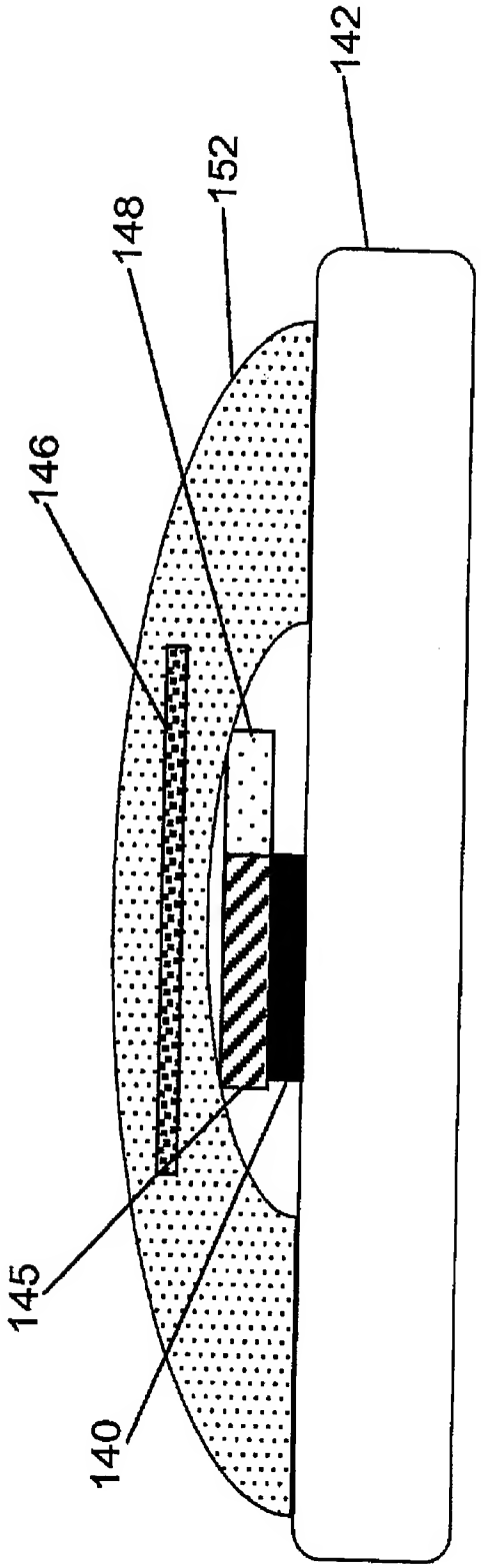

FIGURE 9

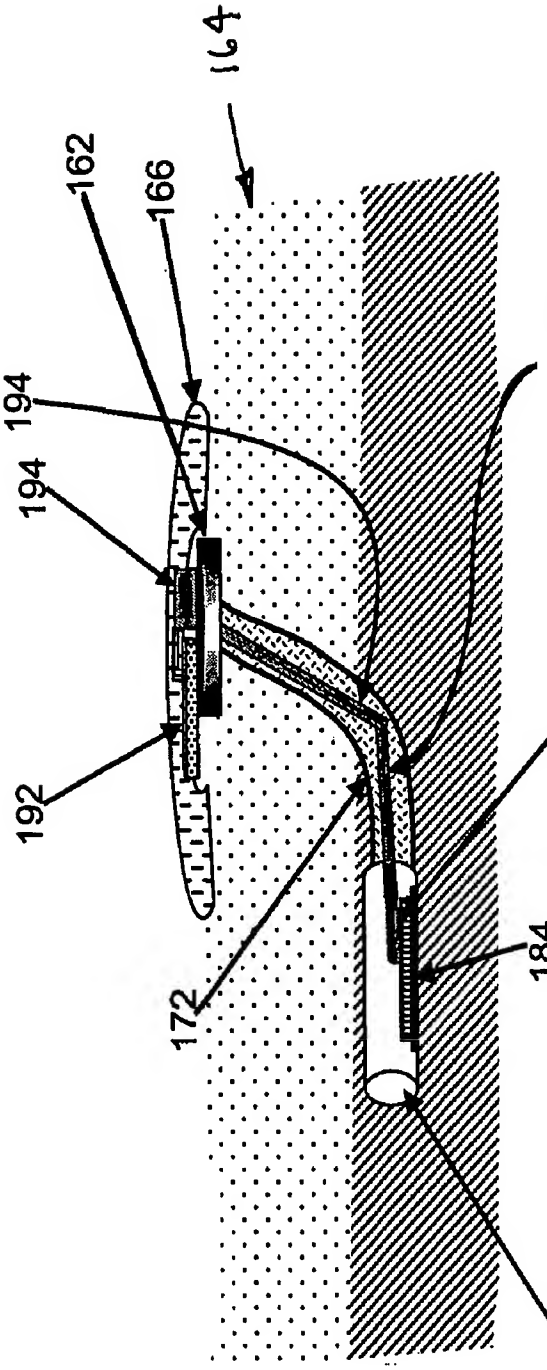

FIGURE 10A

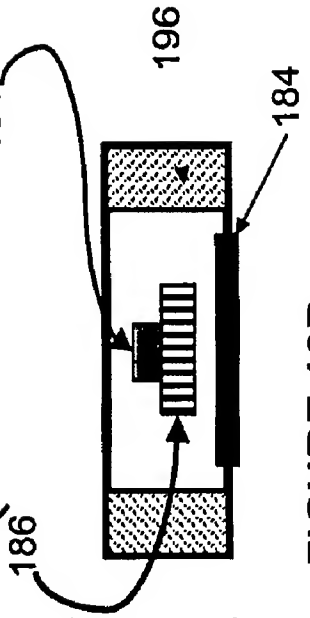

FIGURE 10B

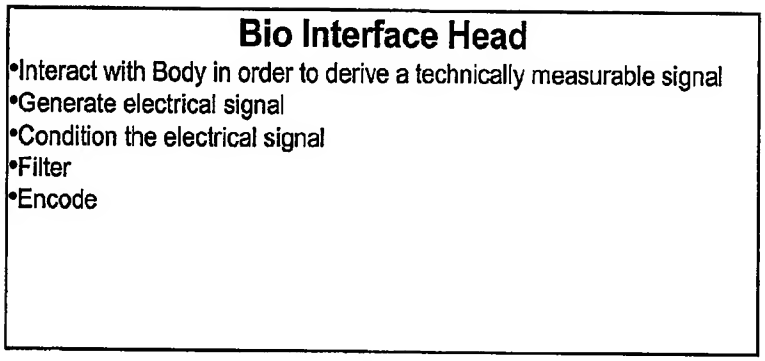

FIGURE 11

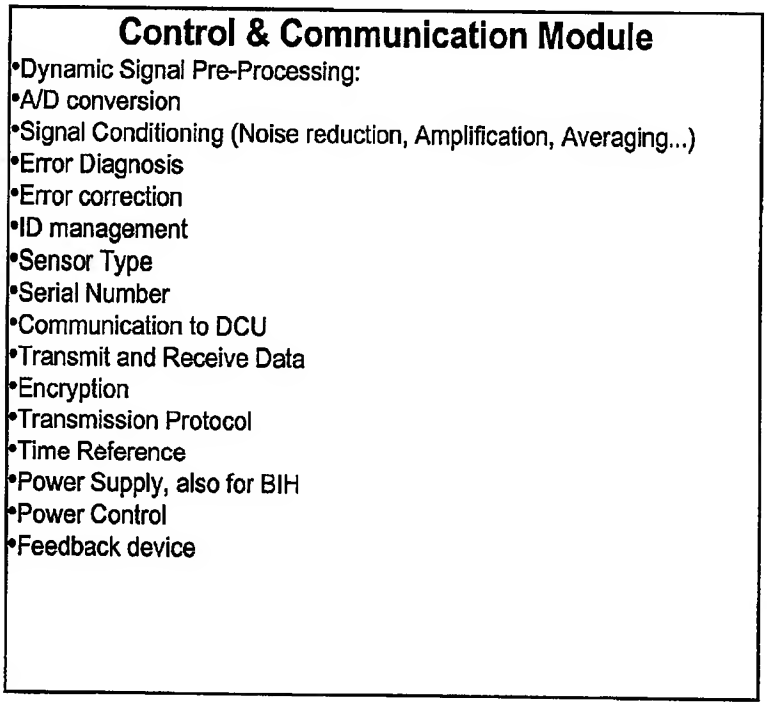

FIGURE 12

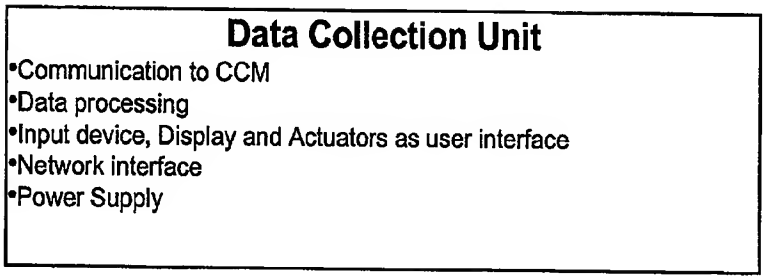

FIGURE 13

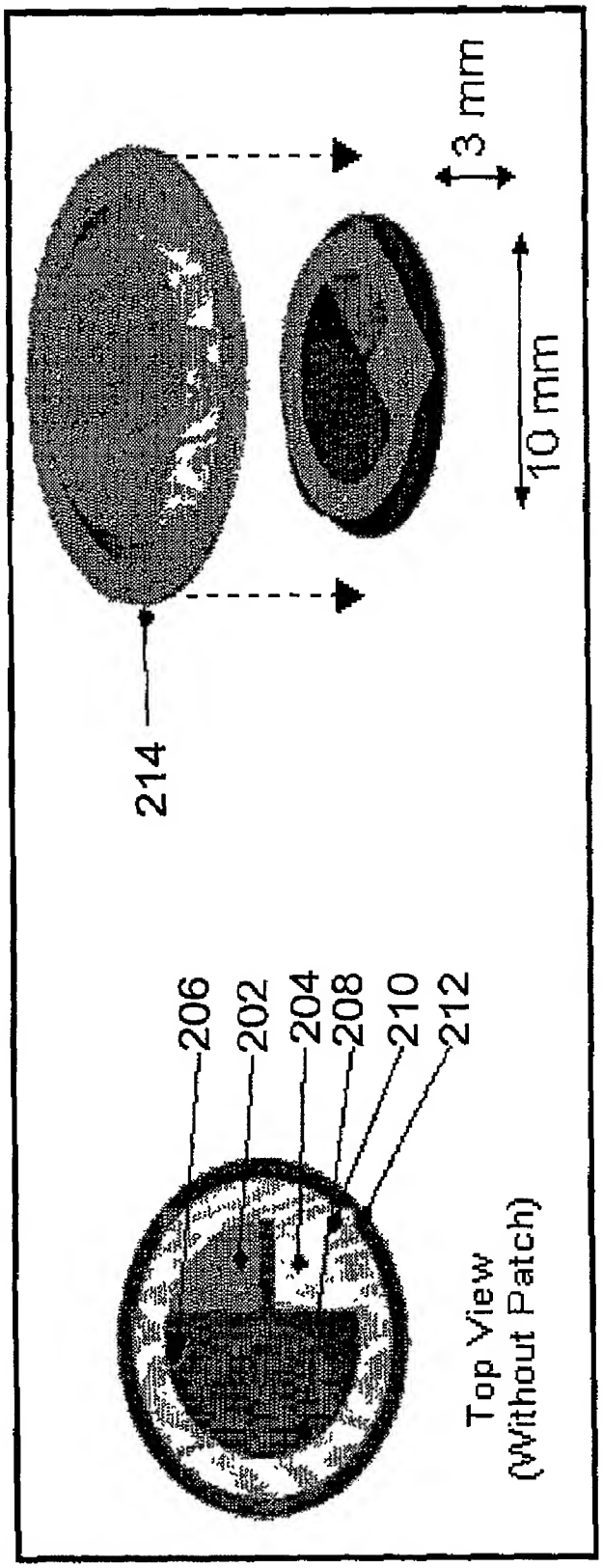

FIGURE 14

GATEWAY PLATFORM FOR BIOLOGICAL MONITORING AND DELIVERY OF THERAPEUTIC COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Ser. No. 60/301,897, filed Jun. 29, 2001.

FIELD OF THE INVENTION

This invention relates to methods and devices for remote or distributed monitoring of physiological states. The invention provides for methods to detect deviations in physiological parameters through the establishment of baseline values, either by direct inspection of compiled data or by computer aided analysis. The device provides for a universal platform for sensors, which may also allow automatic compensation or distribution of devices or bioactive agents at appropriate levels and/or intervals in response to deviations sensed in various physiological parameters.

BACKGROUND OF THE INVENTION

Long-term monitoring of physiological parameters has been particularly problematic to implement. This type of monitoring may be essential in many situations, especially for patients that exhibit transitory physiological abnormalities. The implementation of long-term monitoring can help solve several problems for at-risk patient care such as: 1) allows continuous monitoring, alerting care givers and patients to potential problems while patients are away from a managed care setting; 2) allows true baselines to be obtained, making deviations easier to detect; and 3) allows the automatic collection of important data necessary to determine the efficacy or non-efficacy of therapeutic treatments.

Long-term monitoring is typically easier to accomplish for non-ambulatory patients. There are many examples of devices that monitor physiological parameters in a hospital setting such as electrocardiograms, electroencephalograms, pulse, heart rate, blood pressure, and so on. However, for individuals that lead an active life, very few options presently exist for long-term monitoring of physiological conditions. Most devices only measure periodically and are prone to measurement variations caused by technique, compliance or use. Most often, these devices require a professional to operate and monitor the condition of the device, as well as to assure patient compliance in order to maintain proper functioning of the monitoring instrument. In addition, biocompatibility issues with many of these external devices are numerous, with side effects such as attendant skin irritations, increasing patient non-compliance with the monitoring devices.

Invasive devices can also introduce complications. Although non-compliance and measurement variation issues may be decreased with semi-permanent implantable sensors, biocompatibility issues are even higher. Implantable devices often have a shortened half-life, due to rejection of the device in the patient, accumulation of biological materials on the device themselves or other events, including infection and mechanical breakdown of the device. U.S. Pat. No. 6,092,530 provides a sensor on the implantable device, which monitors accumulation of biological material on the sensor itself, decreasing the need to investigate the state of the device through invasive measures. The sensor is

remotely interrogated by an external device via electromagnetic or high-frequency radio waves, triggering the sensor to transmit encoded data to the external reader device.

Other medical sensors have been described which measure various physiological parameters for remote monitoring. For example, U.S. Pat. No. 5,987,352 to Klein, et al. discloses a minimally invasive implant coupled with a telemetry system that stores triggered electrocardiogram data. This device records physiological events that meet a set threshold parameter, which is subsequently downloaded to an external reader device through external interrogation. U.S. Pat. No. 5,833,603 to Kovacs et al. provides a device for monitoring various physiological parameters and storing identified data. Similarly, U.S. Pat. No. 4,854,328 to Pollack discloses an animal monitoring system, which comprises an implantable temperature sensor, and transmitter, which transmits a signal, upon sensing a predetermined threshold value, to a remote receiver. Because the devices record only data that satisfies a set threshold parameter, it is unsuitable for establishing baseline patterns necessary in detecting low frequency events. Both devices also require an external interrogator device, which prompts the transponder to download collected data to an external recording device.

Other wireless technologies enable measurement of various physiological parameters on externally-based or implanted biosensors. U.S. Pat. No. 5,511,553 to Segalowitz also discloses a device which measures multiple electrophysiological parameters that provide continuous monitoring in a wireless fashion for assessment of cardiovascular condition in ambulatory patients. U.S. Pat. No. 6,175,752 to Say et al. discloses an analyte monitor which measures multiple physiological parameters and provides for continuous monitoring in a wireless fashion. The device also provides for a drug-delivery system to alter the level of the analyte based on the data obtained using the sensor. Although both devices combine the use of biological sensors with wireless transmission of data, it does not appear that they provide for a long-lasting, biologically compatible system that allows continuous feedback and analysis with a network-based system capable of relaying information from remote sensors on a mammlian subject to a central data analysis system. There exists a continuing need for long-term physiological monitoring devices that provide sensors which reduce biocompatibility issues and provides a wireless data-relay system which reliably transmits bioparameter data, allowing continuous or periodic monitoring of a patient's or users physiological state.

SUMMARY OF THE INVENTION

Accordingly, one aspect of the present invention is to address the shortcomings mentioned above by providing for methods and devices which allow the continuous or periodic monitoring of physiological conditions. Physiological parameters are monitored via sensors mounted within a BioInterface Head (BIH), which is linked to a Communication and Control Module (CCM). The CCM controls the BIH function and automatically transmits converted and encrypted information to a Data Collection Unit (DCU) via remote telemetry. The information from the DCU is analyzed and may be forwarded to a remote data management system which will allow access by the measured subject, caregiver or other authorized individuals by remote telemetry or other forms of communication (FIG. 1). An automatic compensation delivery mechanism may also be incorporated into the device, which may deliver therapeutic agents, compounds or other materials in response to detected

abnormalities or fluctuations in various physiological parameters, or to outside authorized command.

One aspect of this invention is a device which automatically and continuously or periodically monitors physiological conditions in vivo using surface or sub-surface implanted sensors linked to CCM's and DCU's. By continuously monitoring physiological parameters remotely or in a distributed environment, baseline or reference data can be obtained, allowing detection of deviations in measured subjects. The device particularly distinguishes itself from long-term monitoring devices currently available by: 1) improving measured data quality by diminishing data variation caused by the user, technique or compliance issues; 2) converting, encrypting and identifying data for further transmission and processing of data; 3) incorporating a wireless transmission signal system (e.g. radio frequency, acoustic or optical) or other remote communication method to allow automatic transmission of data collected from the CCM/BIH assembly to either adjacent or remote CCM's or DCU's; 4) reducing biocompatibility issues associated with implantable sensors with the use of novel biomaterials and devices to decrease the adhesion or encapsulation of the biofluid access port by biological processes; and 5) coupling the wireless signal system to enable a two-way wireless-based control system to allow controlled or automatic delivery of compounds or devices from the CCM/BIH assembly.

In one aspect, the BIH assembly may comprise various types of sensing mechanisms, including thermal sensors (thermoresistors, thermocouples), electrical sensors (EKG, ECG, impedance, frequency or capacitance), optical sensors (photonic wavelength, colorimetric, turbidity), chemical sensors (pH, biomolecules, gases such as CO_2, and other chemical sensors), enzyme-linked sensors (glucose oxidase, phosphatase, coupled substrates (e.g. horseradish peroxidase or alkaline phosphatase and other enzyme-linked sensors)), radiation sensors (gamma, beta and other radiation detectors), magnetic sensors (micro NMR circuitry and magnetic spin state) and physical sensors, such as flow meters and pressure sensors. Alternatively, the sensor may also comprise a MEMS (Micro Electrical Mechanical Systems) or a MOEMS (Micro Optical Electrical Mechanical Systems) sensing device, comprising at least one cantilever beam coated with polymeric compounds for detection of various physiological substances or conditions. The microcantilever beams allow increases in sensitivity and specificity, as compared to currently available technologies, and simplifies detection by coupling the beam to transducers which measure changes in capacitance, resonant frequency, or other techniques used in detecting mass changes in the spring element of the cantilever beam. In still other embodiments, nanotechnology devices may be incorporated into the sensor head or other components of the device for more accurate detection, cellular manipulation and measurement of physiological parameters. In one embodiment the BIH assembly, as well as other components of the system, may contain components micron, submicron or nanoscale in dimension, further lessening the obtrusiveness of the device to wearer.

In another aspect, the BIH assembly of the sensor element comprises materials that permit interaction of the sensor with the host environment. This includes microchannels, gel, fine mesh, screen, membrane, filters or a microporous frit, which permit interaction of sensors to the host environment while maintaining a segregated and sterile environment within the sensing element itself. This tends to extend the life of the sensor by preventing fouling of the biological sensor with macromolecules and other substances that can adhere onto the sensor mechanism.

In accordance with another aspect of the invention, the use of specialized biomedia can be incorporated into the sensing head device and may decrease the exposure of the sensor element to the external environment. This biomedia system may also decrease the adherence of the sensor element onto the host tissue or layer, a large component of the rejection mechanism of biological sensors. Moreover, the use of a biomedia system may lower trauma to the surrounding tissue or layer by providing medium that is physiologically compatible with the host, mimicking the tissue environment in which the sensor is implanted. In yet another aspect of the invention, growth factors, cell signaling and cell adhesion molecules will be integrated into the biomedia system, mimicking the tissue and further improving biocompatibility issues of the sensor implantation into the host species.

In other aspects, the biomedia may have gel-like properties at ambient room temperature, whereupon exposure to higher body temperatures changes the material to a fluid-like state and becomes less viscous. One utility of this gel-like material may be its use as part of a calibration process for the sensor elements. When the sensor is implanted on or into the host, the sensor itself is shielded from the host environment by the gel-like material. As the temperature around the sensor increases, the gel-like material changes viscosity, freeing calibration molecules from the matrix that then enter into the sensor. The sensor can then be accurately calibrated before being equilibrated into the host environment. The bio-media may also be used as a process or method during manufacturing. The bio-media may also provide increased product shelf-life storage by insulating the sensors on the BIH from degradation caused by ambient conditions such as temperature, humidity or other degenerative storage issues.

In another aspect of the invention, the BIH assembly, located on top or within the dermal layer, interacts with the CCM (Control and Communication Module) that is also located on top or within the dermal layer. The CCM interacts with the sensor unit either directly through a physical means (e.g. conductive wire, optical, acoustic or other means) or indirectly using a remote wireless-based signal and control system. The CCM also contains a power supply consisting of either a removable or responder power source. The CCM and the BIH assembly, if located on top of the dermal layer, are attached to the host patient through a bioadherence system, which allows minimal irritation of the outer body surface, thereby tending to decrease rejection and increase the longevity of the BIH and CCM assemblies.

In one particular aspect of the invention, the BIH is monitored externally by direct communication with the CCM. The CCM can automatically, and continually or periodically, download stored converted and encrypted information to a Data Collection Unit (DCU). The CCM may also automatically, and continually or periodically, download stored information to a remote or adjacent CCM in areas where signal transmission may be problematic. Where communication between the CCM and DCU is possible, but not between the DCU and the remote database management system, the DCU may download information to another remote or distributed DCU until communication linkage with the remote database management system can be established. The CCM is also capable of receiving processed information from a remote database management system, DCU or adjacent or remote CCM, alerting the patient or user through a separate communication channel or method, such as through a localized display (e.g. visual, physical or acoustic means (liquid crystal display, organic light emitting diode (OLED) display, magnetically sensitive liquid ink

displays, audio alarm, physical vibrations or paging mechanism)), or telecommunications pathway.

According to another aspect of the invention, the Bio Interface Head (BIH) comprises a release system delivering therapeutic agents, which are administered in response to detected changes in various physiological parameters. The release system contained within the BIH interacts with the CCM and releases therapeutic agents in response to instructions received from the CCM. The CCM can be programmed to directly trigger delivery of therapeutic agents, or can be coupled to an external control circuitry, allowing remote monitoring of a patient's condition and subsequent adjustment of therapeutic agents in order to stabilize various physiological indicators.

While the advantages and features of the invention have been described above, a detailed description of the invention can be found below with accompanying embodiments. These embodiments are illustrative of the many ways in which this invention can be exploited, and further advantages and features will become apparent through the detailed description of the invention and their accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other objects, advantages and features of the present invention will be more readily understood from the following detailed description of the preferred embodiments thereof, when considered in conjunction with the following drawings.

FIG. **1**. Components of the Human Gateway System.

FIG. **2**. Block level diagram of an embodiment of the system, wherein sensor information from the BIH is preliminarily processed by the CCM and transmitted to the DCU and remote database management system. The remote database management system, based on information received by the sensor, is capable of providing feedback analysis to the DCU or CCM or both.

FIG. **3**. Illustration wherein a direct communication linkage is established between the CCM and BIH.

FIG. **4**. Illustration wherein the BIH and CCM are integrated into one component.

FIG. **5**. Illustration wherein a direct communication linkage is established between the CCM and an implanted BIH.

FIG. **6**. Illustration wherein an indirect communication linkage between the CCM and a surface-mounted BIH (FIG. **6**A) or an implanted BIH (FIG. **6**B) is established.

FIG. **7**. Block diagram illustrating the use of more than one CCM to relay data from the BIH.

FIG. **8**. Block diagram illustrating the use of more than one DCU to relay data from the BIH.

FIG. **9**. Partial cross-sectional view of surface-mounted BIH and CCM assembly

FIG. **10**. Partial cross-sectional view of Invasive BIH and CCM assembly (FIG. **10**A) and sensor head assembly (FIG. **10**B).

FIG. **11**. General requirements for electronics in BIH

FIG. **12**. General requirements for electronics in CCM

FIG. **13**. General requirements for electronics in DCU

FIG. **14**. Views of a surface mounted BIH/CCM assembly

DEFINITIONS

HUMAN GATEWAY (HG) Platform—This describes a system of components, devices, data management systems and services necessary to remotely measure bioparameters, collect the data in a wireless remote environment, analyze and summarize the data and provide access to this data by the mammalian subject, clinician or authorized third party. In addition it may include a two-way secure communication system enabling a mammalian subject and clinician to remotely communicate diagnostic knowledge and/or actions.

BIH—BioInterface Head. May include sensors, interface or sensor mounting features, data communication features, and structures for limiting movement or ensuring placement on the measured subject of the sensors.

CCM—Control and Communication Module. Contains circuitry and means necessary to receive signals from the BIH, other CCM's and DCU, process those signals and/or transmit them to a DCU, BIH or another CCM.

DCU—Data Collection Unit. Contains circuitry and means necessary to receive and send signals from at least one CCM, DCU or external transmissions from other telemetry systems e.g. cellular, pager, fixed telemetry or other telemetry systems.

Biomedia—Specialized medium to decrease exposure of the sensor element to the external environment. Biomedia may consist of material that is biologically and physiologically compatible with the host patient, whereby the properties are such that external calibration standards or markers are incorporated into the device and are released upon insertion of the device into the host patient. Biomedia may consist of any physiologically compatible reagent including, but not limited to: hydrogels, agarose, gelatin, starches, or any other natural or artificial polymeric compound.

Body surface—Body surfaces covered by epidermis or other related cell types and exposed to the external environment, either continually or transiently without piercing or otherwise penetrating the integrity of this surface. Examples of these surfaces include but are not limited to: skin or internal surfaces such as the mucosal surfaces that are found in the mouth, nasal passages, or other body passages.

Conditioned Data—data received from the BIH and processed to remove extraneous noise or signals, as well as other procedures for enhancing signal quality and transmission.

Continuously—Application-dependent frequency of measurement not requiring user intervention.

Database Management System—Computer-based management system for processing, storing and summarization of sensor data to determine physiological parameters of the mammalian subject, detect deviations or abnormalities in the physiological parameters, determine the mode of action in response to an analysis of the physiological parameters or any other analysis and processing of the data necessary in evaluation of the mammalian subject. Control instructions in response to the processed data may be transmitted back to the mammalian subject or other authorized personnel through a computer-based or wireless communications means.

Data Transmission Device—personal digital assistant, pagers or other devices capable of data transmission or receiving information or instructions.

Encrypted Data—asymmetric or symmetric encryption of data received from sensors into encrypted text. Allows the transmission of data and subsequent receipt of the same to be performed on any available control and communication module or data collection unit.

Mammalian Subject—the human, animal or other organism in which measurements are being collected.

Periodically—User or system-controlled measured frequency.

Processed Data—error diagnosis and/or correction and analog to digital conversion or digital to analog conversion, as well as other means for enabling or enhancing the transmission of data.

Remotely located—not in physical connection to mammalian subject.

Subdermally—located beneath the dermal layer surface.

Subcutaneously—located beneath the skin surface.

Sensor—Mechanical, electrical or optical sensing devices that measure information such as physiologically relevant information (e.g. temperature, pressure, EKG, ECG, pH, biochemicals, biomolecules, gases such as CO_2, and other chemical parameters, enzyme-based parameters, radiation, magnetic and physical parameters, such as blood flow, blood pressure or other physical parameters), or other information (e.g. body positioning, GPS location).

Wireless means—radio frequency, acoustic or optical means for transmitting and receiving information.

DETAILED DESCRIPTION OF THE INVENTION

The devices and methodologies of this invention provide a platform for the mounting of biosensor modules useful for the monitoring of bio-parameters including, but not limited to: physical measurements; e.g. temperature, motion, electrical, conductivity and pressure; (Wheatstone bridge measurements), chemical measurements, e.g. concentration of salts, drugs, metabolites, hormones, and pH; and bioactive assays, e.g. testing for the presence or absence of antibodies, or other biomolecules or bioactivities from within the mammalian subject. Once obtained, these data are transmitted from the BIH components to the CCM for compilation and response. Overall the device can be designated as a HUMAN GATEWAY (HG) platform (FIG. **1**). It is a unique feature of this invention that the data collection is automatic, autonomous and unobtrusive. In addition, it may be linked to a two-way communication system, remote storage or data analysis system.

It is another unique feature of this invention that it may serve as a platform onto which one or more sensors can be incorporated as needed and as sensor systems change. That is, it is a feature of the invention that the HG (HUMAN GATEWAY) platform provides the basic infrastructure for a universal bioparameter monitoring platform. Another feature of the invention is that the device may also serve to provide metered release of devices or delivery of suitable agents (e.g. therapeutics) to the body through suitable components incorporated within the BIH. This invention features a linkage between the BIH, containing at least one sensor module, CCM, and a remote DCU by use of a data relay system utilizing a wireless-based data transmission system (e.g. RF, acoustic or optical). This wireless-based system may be used to relay biometric data and control signals from the BIH to the CCM as well as to and from the data collection unit (DCU).

In a preferred embodiment of the invention (FIG. **1**), the HG is comprised of three principle components. The first component **10** comprises the BioInterface Head (BIH) and Control and Communication Module (CCM). The second component **30** is the Data Collection Unit (DCU), and the third component **50** is the Database Management System. The CCM and DCU components function to relay both bio-parameter measurements and signals to and from sensor modules mounted or otherwise attached to the BIH, which may be attached to the CCM.

In operation (FIG. **2**), the BIH **11** obtains bioparameter data from sensor **12** measuring appropriate bodily conditions, states or composition, e.g. temperature, pH, or levels of defined biomolecules. The BIH **11** then communicates this data to the CCM **15**. The CCM contains optimized circuitry necessary for basic data processing **14**, signal processing **22**, and data transmission **17**. The CCM **15** relays the data stream to an adjacent DCU **30** unit. The DCU **30** units may be fixed at defined locations (e.g. fixed intervals in building corridors) or portable (e.g. worn or held by the person being monitored). The CCM **15** may convert the biosensor data stream from an analog signal to a digital signal **21** (depending upon the sensor utilized), perform preliminary signal processing **22**, display a limited form of data (i.e. current measured value) and encrypt and encode identification tags **16** to the converted and processed data. The DCU **30** can receive preliminarily processed data **36**, perform necessary additional signal processing **34**, compilation of subsequently transmitted data sets **32** from the CCM **15** and store data **38** as necessary. The DCU **30** may periodically transmit **36** the data to a remote database management system **50** for further signal processing **52** (decryption, identification), analysis **52**, summarization **58**, storage **56** and/or action **59**. The database management system **50** may also, in response to the summarization of data received, feedback either to the DCU **62**, CCM **64** or both.

In a preferred embodiment (FIG. **3**), communication of the BIH **11** and CCM **15** is through a direct physical link **76** to the BIH **11**. Examples of the means by which the CCM **15** can be connected to the BIH **11** are: conductive wire, optical fiber, tape or nylon filaments, silicon microvia channels or other methods that physically link the BIH to the CCM.

Alternatively (FIG. **4**), the BIH **11** is linked **78** to the CCM **15** fabricated assembly such that no clear delineation is visible between the two components. In this embodiment, both components may reside on the surface of the body.

In a second variation of this embodiment (FIG. **5**), the CCM **15** is physically linked **82** to the BIH **11**, however, in this variation, the BIH **11** is located below (or within) the body surface **84** whereas the CCM **15** resides on the outside surface of the body. The location of the implanted BIH may be sub-dermal, or located within deeper tissues or layers or within organs of the body.

In yet another variation of this embodiment (FIG. **6**), the CCM **15** is not physically linked to the BIH **11**. The CCM **15** resides on the outside surface of the body **84**. The BIH **11** is located either on the outside surface of the body (but not physically linked; FIG. **6**A), or is implanted below the surface (but not physically linked; FIG. **6**B). The CCM **15** and BIH **11** communicate through a wireless means **86**, such as electrical, optical or acoustic transmission. The location and manner of the mounting of the CCM and BIH on the host body are determined by the application or bioparameters to be measured.

More than one CCM/BIH assemblies may be employed for measurement of physiological bio-parameters. Bio-parameters of the mammalian subject are obtained by a plurality of BIH assemblies and collected with intra-device communication, signal monitoring and analysis, e.g. signal/time differential sensing of electrical impedance between multiple assemblies. Variations of this approach would be the inclusion of multiple multifunctional CCM/BIH assemblies for data collection and transmittal.

One feature of the present invention is that multiple CCMs may be employed to provide a more robust commu-

nication of data to databases if a DCU or mammalian subject is out of coverage range or experiences some type of data transmission interruption or interference (FIG. **7**). For example, a CCM #1 **92** located on a subject transmits **94** the collected data from BIH #1 **93** and processed bioparameters to a CCM #2 **96** located on an adjacent mammalian subject. CCM #2 **96** would then transmit **98** data received from CCM #1 **92** and its own collected bioparameter data from BIH #2 **97** to an available DCU **100**, which would then upload **104** both data sets to a remote database management system **102**. The transmitted data from both CCM #1 **92** and CCM #2 **96** will be encrypted and encoded to ensure that the information is secured and transmitted to authorized communication devices only. This example may be extended to include two or more CCMs to relay the data to a DCU.

Improved communication between devices may also be accomplished by an alternative embodiment (FIG. **8**), where multiple DCU's **118** and **128** are used to relay the bioparameter data to a remote database management system **134** if the mammalian subject is out of coverage range or experiences some type of data transmission interruption or interference. In this example, a CCM #1 **112** receives bioparameter data from BIH #1 **114**. CCM #1 **112** transmits **116** the bioparameter data to DCU #1 **118**, which in turn transmits **122** the signal to DCU #2 **128**. DCU #2 **128**, which also receives **126** data from BIH #2 **124** through CCM #2 **122**, transmits bioparameter data from both BIH #1 **114** and BIH #2 **124** to a database management system **134**.

Improved communication may also be achieved with the use of multiple CCMs receiving appropriately coded signals or data from a transmission source other than a DCU. Such a signal may take the form of a radio transmission sent by common carrier transmitters, e.g. commercial radio stations, which may provide an alternative means to communicate to CCM assemblies. Such a communication means may prove useful for reaching one or more measured subjects such as the need during natural disasters or civil emergencies to ensure proper functioning of BIH/CCM assemblies.

BioInterface Head (BIH)

The Bio Interface Head assembly picks up one or more external or internal measured parameters, which may include physiological parameters, biomolecules or foreign agents, and transforms them into an easily processable signal, usually electrical or optical. The BIH is comprised of several components. These may include, but are not limited to, sensors, interface or sensor mounting features, data communication features, and structures for limiting movement or ensuring placement on the measured subject of the sensors. A preferred embodiment of the invention includes within the BIH at least one sensor which measures physiological parameters, e.g. temperature or pressure. Surface temperature sensors which can be placed on the thorax, armpit, extremities or other parts of the body surface (Exacon, Inc., D-SFL-1 multipurpose temperature sensor, Wuntronic glass probe NTC Thermistors Series SP or other commercially available thermistor) can be mounted onto the BIH head for temperature measurements. Other sensors may also be included which measure EKG, ECG, pH, biochemicals, biomolecules, gases such as CO_2, and other chemical parameters, enzyme-based parameters, radiation, magnetic and physical parameters, such as blood flow, blood pressure or other physical parameters), or other information (e.g. body positioning, GPS location).

The measured data signal from the sensors may be conditioned at the BIH assembly to enhance the transmission to the CCM. Examples for such conditioning are amplification, filtering or encoding. The signal is then transmitted to the CCM. In cases where the BIH is integrated into the CCM, the connection may be very short. The connection may consist of an on-chip connection, which would minimize the distance between the CCM and BIH.

Depending upon the application, the BIH may comprise a contiguous unit with the CCM whereas in other embodiments, the BIH may be a separate unit from the CCM, linked by either electrical, optical or other means to convey data between the CCM and the BIH. The BIH may be a replaceable unit connected by physical or wireless means to the CCM. This feature permits the ability to replace the BIH with either a new, different or replacement BIH assembly while maintaining the same CCM. In addition, one design feature desirable in certain applications is that if the CCM or BIH is abruptly moved or otherwise displaced, it disconnects from the BIH such that the sensor system, including those forms transdermal in aspect, remain intact and non-moved.

The BIH, in addition, may also contain replaceable, disposable sensors mounted within or otherwise attached to the BIH mounting unit. This feature permits the ability to replace sensors within the BIH with either new, different or replacement sensor units while maintaining the same CCM-BIH assembly.

The BIH may utilize surface or non-invasive sensors for obtaining bioparameter data, such as temperature or pressure. Alternatively, the BIH may employ or mount sensors designed for obtaining subdermal (or further within the body) measurements. The form of the BIH will accordingly differ depending upon the application, which governs the sensor selection.

The BIH may incorporate sensors that measure and/or transmit data either mechanically, electrically, photonically or by other means. Addition of circuitry or other technology, e.g. photomultipliers, may be added based upon signal-to-noise analysis with each type of sensor.

In addition, the use of photonic systems, e.g. vertical cavity semiconductor laser (VCSL)—derived excitation, coupled to photodetector pickup utilizing optics, e.g. fiber optics, or waveguides, for signal transmittal from the sensor head may be used to communicate between the CCM and BIH. Again, dependent upon signal strength, it may be necessary to locate some of the signal processing functions on the BIH. A photonic coupled system may be less noisy than a corresponding electrical platform, making photonic signaling between the BIH and CCM more desirable in specific situations.

Compatibility of the BIH to the environment (e.g. biofluids) for extended periods will also factor into the design of the sensor platform. Depending upon the environmental conditions, coatings (e.g. silicone, epoxy, synthetic polymers or other materials) or other approaches may be incorporated onto the sensor platform to extend BIH and/or CCM lifetime or to enhance biocompatibility.

A surface mounted BIH, as illustrated in FIG. **9**, is a platform capable of measuring bioparameters from the measured subject with sensors. In simple situations, the sensors **140** are in contact with the uppermost dermal or surface layer **142**. An example of this can be found for surface temperature sensors placed on the thorax, armpit, extremities or other parts of the body surface (Exacon, Inc., D-SFL-1 multipurpose temperature sensor, Wuntronic glass probe NTC Thermistors Series SP or other commercially available thermistor). In other situations, microsensors, such as microneedles utilized for conducting heat to temperature

sensors, may be extended in a transitory fashion from the surface mounted head in order to obtain readings.

The unit itself may be packaged along with the CCM **145** as shown, or may be separated from the CCM but linked to the CCM via conductive wire, optical fiber or other data transmission methods. Sensor systems, mounted within the BIH, may deliver electrical, optical or other type of data signal to the CCM depending upon the sensor type utilized. The unit will also include a transmission and receiving device **146**, as well as a power source **148**.

Mounting the BIH onto the surface may be done by adhesive patch **152** or by other methods which attach the assembly to the surface or any defined location on the body, e.g. on the skin, tooth surfaces, oral cavity or within other body cavities.

An invasive BIH (FIG. **10**) is designed to serve as a platform for biosensors monitoring bioparameters internally or below the surface of the body. It is also designed to link the data to and from these sensors to the surface mounted CCM. One feature to the invasive BIH is its function of linking subdermal (or deeper) sensors to the CCM while minimizing infection and rejection by the host. As such, it may contain several aspects to a design.

An invasive BIH may typically have three main tasks. The first task is to serve as a path or avenue to allow the sensors access to the internal environment, including internal biofluids (e.g. blood, lymphatic fluids, ductual fluids, or any other fluids produced by the body). This environment may be subdermal or located deeper within the body, e.g. the peritoneal cavity, intramuscular, or organs. The second is to anchor or locate a signal transmission device and the third is to hold a sensor or mount for a replaceable, insertable sensor assembly.

These features or tasks are illustrated in FIG. **10**. There may be other designs and structures which perform these tasks that are also possible, and this embodiment is not intended to limit the scope of this invention. This design has four main components. The first of this is the external mounting ring **162**. This feature is to be made of an inert, hypoallergenic material, e.g. stainless steel, nylon or any other material which does not cause an allergic reaction in the body. Mounting points may be contained on this ring for the external portion of the replaceable, insertable sensor assembly. Anchoring this ring to the dermal layer **164** may be done by utilizing both adhesives **166** and the physical compression of the tissue surrounding the transdermal portion, or any other method which will anchor the ring to the dermal layer. The adhesives employed may be both conventional biocompatible synthetic adhesives as well as materials utilizing the bodies' own ability to form fibrous, contained structures contiguous to the dermal layer (the equivalent of a common scab). This latter point may be accomplished by coating the lower aspect of the mounting ring with appropriate growth factors, adherence molecules and attractants, such as prothrombin activator, vitamin K, thrombin, fibrin, keratinocyte growth factor, activin, proteoglycans, cytokines, chemokines, TGF-beta, TNF-alpha, VEGF, PDGF, FGF, PAF, NGF, IL-4, IL-8, Insulin-like growth factor, integrins, laminin, fibronectin and other factors which promote the cutaneous wound-healing mechanism and formation of an epithelial-like structure around the mounting ring.

Extending below the mounting ring is the second component (transdermal conduit **172**), which is a structure (e.g. tube or filaments), that serves as the guide for the insertable sensor assembly. The transdermal conduit is a semi-permanent tube or structure that may be inserted by a clinician and is not intended to be routinely removed or replaced by the measured subject or clinician. In most embodiments, this tube is flexible, hypo-immunogenic and possesses one or more hollow cores. A variety of materials have been employed in the health care industry for use as catheters, including silicon polymers, which have the appropriate ductility and biocompatibility. If necessary, the outside wall may be coated with additional polymers to increase biocompatibility and minimize the possibility of rejection, e.g. polyethylene glycol or other related polymeric materials. To provide additional mechanical strength, a laminate interior comprised of nylon or high strength fiber mesh may be added, e.g. KEVLAR (a nylon laminate), which adds strength while maintaining the required flexibility. Flexibility and ductility are elements for comfort and acceptance of this implant technology.

At the end of the transdermal conduit is the third component, the sensor mounting head **182**. This mounting head may also facilitate insertion of the implantable BIH assembly. The mounting head will also be composed of rigid biocompatible materials, such as nylon or other materials that would increase the rigidity of the structure. However, in order to minimize fibrous growth in the region of the implant, it may be coated with appropriate adhesion biomolecules and/or growth factors to mimic the surrounding environment and aid in the integration of the device into the surrounding tissue. In addition, anticoagulation aids (e.g. heparin or other pharmaceutical anti-coagulants) may be present to prevent the adhesion of platelets or other clotting/rejection factors onto the sensor head. The integration of the head into the surrounding tissue may be necessary in order to minimize physical disruption of adjacent cells during routine motion on the part of the individual, thereby lessening encapsulation of the device by fibrous tissue as part of the body's rejection mechanism.

Contained within the head is the fourth structure or component, the biofluid access port **184**. This feature provides the means for biofluids to pass into the device for analysis while simultaneously avoiding contamination from the outside environment. To accomplish this, a fine mesh, membrane or frit, or any other material which would provide a barrier for the sensor head, may be employed to prevent the transference or transmission of pathogens into the body. Certain micro-structures, e.g. MEMS or MOEMS based structures, formed with microvias, micro-sphincters, microvalves, micro-openings, or composite nanostructures having a porous character, e.g. a mesh, contained within a surrounding silicon chip can provide the necessary exclusion of particles while allowing fluid and small molecule passage for testing. In addition, this component will have the necessary structural features for packaging within the rigid head component. In certain applications, the access port itself is part of the sensing system, e.g. a pressure sensitive device or thermal sensing unit. The biocompatibility issue has been a significant challenge in prior devices. In particular, cellular debris in the vicinity of the access port might lead to the development of a rejection response or render the sensor ineffective. To minimize this risk, flushing of the vicinity in the region of the access port may be necessary to remove cellular debris periodically. Flushing can be performed either manually by the user, or automatically through the use of channels or compartments which release saline or other physiologically compatible solution upon the sensing of occlusion, rejection or other factors which may diminish the intended performance of the device.

One approach to minimize performance degradation of the device is by the addition of biocompatible fluids **196**, e.g. blood substitutes, physiological saline, or other physiologi-

cally compatible solutions which may contain bacterio-static agents into the interior of the transdermal conduit. These fluids would either back flush occluding material out of the transdermal conduit or, by virtue of the hydrostatic pressure generated by inserting the BIH assembly **194** into the conduit, force the small amount of cellular debris adjacent to the access port into the surrounding extracellular fluid or interstitial space aiding the body's own mechanism to flush the material away. Other approaches include the addition of appropriate adhesion factors (integrins, laminin, fibronectin and other adhesion factors) to augment the integration of the access port to the surrounding cells, coupled with the use of other microdevices, e.g. MEMS or MOEMS, that remain sealed until activated. Upon activation (based upon communication from the outside system through the BIH assembly), vias open up within the micro device, resulting in micropassages into which extracellular fluid may flow. Micron scale "scrapers" within the microdevice may also be employed in conjunction with flushing to remove debris and gain access to interstitial fluid. Additional approaches, e.g. the use of electrical, or photonic forces, or chemical agents, may also be employed to sweep the charged biomolecules forming the cellular debris away from the access port and/or improve access port function. All of these approaches may be synergistically applied to provide access to biofluids for monitoring. A valved structure may also be utilized to control the quantities and sterility of the biocompatible fluids **196** used to flush the transdermal conduit. This valved structure may be created by insertion of the replaceable BIH assembly **194** into a valve means, which would aid in controlling the added biocompatible fluids **196** as well as regulate backpressure from infiltrating biofluids into the biosensor head **182** and the transdermal conduit **172**.

To aid with the manufacture, storage, in-field calibration and insertion of the BIH, a biocompatible hydrogel or similar substance may be used to coat or encapsulate the BIH assembly **194**. The conduit **172** and head **182** may also be filled with this hydrogel. The hydrogel may contain preservatives, anti-inflammatory agents, anticoagulants, bioactive agents, e.g. growth factors, cytokines or other bioactive agents, and antibiotics or antimicrobial agents. A form of hydrogel (e.g. select agarose gels, carrageenan gels, collagen gels, or other biocompatible synthetic or natural gels) may also be employed which exhibits the property of either being gel or liquid in nature in a temperature-dependent fashion. In particular, at or around room temperature the material has high viscosity and is gel-like in nature. When raised to body temperature, the material becomes fluid and is absorbed by the surrounding tissue.

Once the transdermal conduit **172** is inserted through the skin or outer membrane, a BIH platform **194** may be passed down through the center core and positioned at the sensor mounting head. The action of inserting the BIH assembly **194** may be performed by a physician, other trained personnel or the mammalian subject directly to replace or change the BIH as needed or as desired. In inserting the BIH assembly **194** down the transdermal conduit **172**, biocompatible fluid **196** containing antibiotics and other agents designed to facilitate biocompatibility, anti-inflammation, system sterility and enhance biomolecule access to the sensor may be introduced. This may be accomplished by having a small reservoir of fluid attached to the BIH assembly **194** and upon application of external force, e.g. manually squeezing the reservoir or any other means of depositing liquid, the fluid is forced down into the transdermal conduit and flushes the conduit, head assembly and access port. Alternatively, the BIH assembly being introduced may have a hollow core through which the fluid may flow, and excess fluid will either pass through the BIH into the surrounding tissue or back up the conduit where, by use of backflow valves, a sterile solution is preserved within the conduit and head assembly. In yet another embodiment, other forms of gels, e.g. Pluronic F-127, which are liquid at room temperature but gel when elevated to body temperature, may be utilized to flush the transdermal conduit **172** and then, upon gelling, provide a barrier to contamination as well as some degree of structural support to the transdermal conduit **172** and sensor mounting head **182**. In yet another embodiment, the BIH can be an integral part or mounted permanently within or on the outside aspect of the conduit/head assembly.

In certain applications and embodiments, the mammalian subject's own bioenvironment, e.g. a rejection response to foreign objects or materials, may be employed to remove the implanted BIH. That is, the BIH may be composed in part or entirety in materials having finite lifetimes within the body. At the end of the anticipated lifetime, a biocompatible coating would dissolve or degrade, exposing a non-biocompatible surface underneath. Alternatively, components of the BIH may be comprised of materials, e.g. collagens, that would be absorbed by the body over time. In other variations, agents to facilitate rejection, fibrous tissue growth or other means of isolating the BIH by natural mechanisms, may be added through the transdermal conduit **172** to end the BIH's lifetime within the measured subject.

The BIH sensor head **182** will signal or otherwise indicate the type of sensor employed as well as a unique identifier to the CCM **192**. The CCM **192**, in turn, may communicate this information back to the DCU such that the data stream is analyzed for the correct physiological parameter and the identity of the individual is linked to this analysis.

1.1.3 Independent Implanted BIH

An independent implanted BIH is similar in concept to the invasive BIH described above with similar concerns about biocompatibility, biofluid sampling, etc. One feature difference is that the independent implanted version does have a wireless means to the CCM. The entire device or package will be inserted, maintained and removed by qualified personnel, e.g. physicians, licensed nurses or technicians.

In order to communicate biosensor data, the independent implanted BIH assembly may include the necessary features from the CCM to enable communications with the DCU or will have a wireless communication link to another CCM assembly (which may be surface mounted). In the former situation, the design of the device will include both features of the implantable transdermal conduit and head assembly, BIH and CCM as an assembly. In the latter case requiring data communication to another CCM assembly located elsewhere, a number of additional features such as power source, data transmission, signal processing, and signal encryption capabilities may be built into the BIH assembly. Possible power sources for the BIH include batteries or responder (RF) technology. Alternatively, the measured subject's own energy, e.g. motion, internal chemistry, including ATP molecules, glucose, or other energy supplying compounds, or osmotic pressure, may supply the energy necessary to power the implanted BIH.

1.1.4 BIH Delivery System

The delivery of various compounds and materials, including, but not limited to: therapeutic agents; molecular scale sensing devices or materials; bioactive substances; enzymes; proteins; gene therapy agents; viral-based bio-agents; and/or micro- or nano-scale devices or materials; may also be accomplished in certain embodiments using the BIH. These

materials and/or devices may be delivered for a variety of purposes, including, but not limited to: the relief of detected conditions; for preventative treatments; and as mobile sensors, detectors or other aids to diagnosis, treatment or measurement.

The reagents, materials, compounds or devices to be administered may be stored within reservoirs or other containment methods within the BIH and/or CCM assembly. The materials, compounds, devices, etc., may be stored in either biologically active or inactive states. The storage form may include aerosols; compressed gases; liquid storage, e.g. suspensions, solutions or gels; and/or dry forms of storage, e.g. powder, granules or films.

Upon receipt of appropriate data and instructions, the CCM will direct the release of some portion, e.g. all or a fraction, of the material from storage in the BIH and/or CCM for delivery either to the surface of the measured subject or below the surface. In the latter case, transdermal delivery systems may include microprobes extending into or below the skin or other outer membrane, or utilize the transdermal conduit and access port of the invasive BIH assembly. In other embodiments, the storage area and/or release site may include locations or sites located on features built into the head or outside aspect of the BIH/CCM assembly. The delivery site and mechanism may also utilize microstructures, e.g. MEMS or MOEMS-based systems, integrated into either the BIH or CCM and may have micro-valves, microchannels, ports and switches.

The delivery mechanism may include, but is not limited to: fluid pumping; mechanical insertion; chemical reactions, e.g. production of gases or pressure to aid delivery; or electrical means, e.g. ionophoretic transport. Alternatively, the delivery means may include the removal or dissolving of protective layers from regions of the BIH upon instruction from the CCM, exposing the bioagents, materials or devices underneath. The bioagents, materials, or devices to be delivered may be mixed with additional fluids or reagents, e.g. water, physiological compatible buffers and components, dimethyl sulfoxide or other solvents, to facilitate generation of active materials or the absorption or uptake of the materials, compounds, etc. by the measured subject. Once added, the delivery system may signal the CCM as to the addition of the compounds, materials or devices or the addition may be monitored by sensors detecting either the agents directly or indirectly through bioparameters.

Control and Communication Module (CCM)

The CCM is the assembly which links the BIH and the DCU (Data Collection Unit). Typically, the CCM receives data from one or more BIH assemblies and transmits the data to the DCU for further processing. The CCM is also capable of receiving information or instructions from the DCU, another CCM or other communications device. Components comprising the CCM (Hardware or Software; FIG. **12**) may include but are not limited to, the signal receiver from the BIH assembly, e.g. electrical, acoustical or photonic signals, a filter to remove extraneous signal and/or noise, memory buffer, analog to digital (A/D) conversion, error diagnosis and/or correction, signal encryption and identification coding, power supply, power supply control, reception/transmission protocol, internal time reference and a means to convey the digitized data to the DCU, such as electrical e.g. radio transmission (RF), acoustic or optical transmission. Individual components comprising the CCM may vary depending upon the type of sensor used, the type and strength of the signal from the sensors, the transmission environment and the availability of DCU's or other receiving devices for transmitting and receiving data or information.

In use, the CCM may take the form of a multifunctional chip assembly mounted onto an adhesive strip or other adhesive material for ease of attachment onto the measured subject. Alternatively, the CCM might be placed onto a device, a strap or integrated into clothing or apparel. In some circumstances, it may be advantageous to mount the CCM internally, e.g. invasively or within a body cavity, in order to minimize device removal and to facilitate use by increasing compliance.

The CCM may be at least one IC (integrated circuit) assembly which may include the following functionalities on-board, depending upon the application and sensors used: A/D signal conversion, signal filtering, memory (Flash RAM/ROM, EEPROM, or other means to store data), controller (including, but not limited to CPU processing, custom microprocessor, one-time programmable microprocessor (OTP), multi-time programmable microprocessor (MTP), field programmable gate array (FPGA), programmable logic controller (PLC) or other types of controllers that are available depending upon the available technology (nano-controllers, optical relays or electrical arrays)), data binning, data transmission encryption and a unique identification (ID tag) as well as functions that were described previously for the CCM, (such as a power supply and antennae for wireless signal transmission and reception to and from the DCU). These functions may be integrated onto a single chip, comprising silicon, gallium or germanium, depending upon the available technology. It may be incorporated into an adhesive patch or device to be worn by the individual to minimize size or bulkiness and maximize comfort.

Modifications to the CCM assembly for adaptation to the implanted sensor platform include but are not limited to the ability to incorporate a bio-fluid reservoir and snap-off mounting to prevent dislodging the transdermal conduit and BIH if the CCM or patch is violently jarred or displaced. Dependent upon the application, the BIH may also be directly assembled onto the CCM assembly in order to reduce the cost and size of the product and improve signal reception from the BIH.

In operation, the CCM receives at least one signal from the BIH. The CCM may amplify the signal through the use of an automated gain control or other means of amplification (e.g. operation amplifier). An analog to digital (A/D) conversion of the received signal from the BIH may be performed if necessary. Other pre-processing methods, such as filtering or signal averaging, may be employed to improve the signal-to-noise ratio. The method employed depends on the type of sensor or application used. The pre-processing also may include error diagnostics (electrical system diagnostics, impedance and other error diagnostic protocols) to detect a problem in the CCM or BIH assemblies, or application, such as communication and/or sensor problem, e.g. a broken wire or an internal sensor fault. This function assures that no erroneous data is generated due to a sensor fault or communication interruption/failure. An error correction algorithm may also be incorporated to enhance the measured signal quality.

BIH and sensor identification (or ID management) is an attribute of the HG system. In particular, the ID management function ensures increased accuracy in sensor type employed and appropriate data tracking and handling to the measured subject. This also enables the DCU to selectively receive information from CCM's that have been addressed to this DCU. ID management provides information about a

particular BIH assembly features such as the sensor type or serial number to the DCU. This information may enhance the data communication reliability and identification of measured subjects in a densely distributed application such as a hospital or assisted living environment.

The pre-processed signal is transmitted from the CCM to the DCU. This transmission may be encrypted using unique encryption algorithms to protect the data and allow security of transmission, especially where multiple CCM, DCU or both are used to relay the information. Furthermore, the transmission protocol may include elements, such as differing frequencies, modulation e.g. frequency hopping spread spectrum (FHSS), direct sequence spread spectrum (DSSS), timing, handshakes e.g. check sums. The transmission may be one-way or two-way, depending upon the need for feedback of processed data or information to the mammalian subject. The CCM may include hardware to enable transmission and receipt of signals from one or more BIH, CCM or DCU assemblies.

The CCM may include a time reference, such as an internal clock, for those applications which require measured data to be correlated based upon a time (relative or absolute) or expiration of time. This is important for many medical applications like ECG or heart rate measurement. In addition it may assist in the analysis of data based upon the frequency of a particular measured event's occurrence or the absolute time when a measured event occurred. It further assures correct communication timing necessary for monitoring of physiological parameters.

A power supply is essential for the operation of the BIH and CCM assemblies. It is preferably integrated into the CCM assembly. It may power the BIH if power requirements exist, e.g. MEMS head assembly or active sensors. Two possible solutions are a battery or a responder circuit that is powered by an electromagnetic field e.g. inductively or capacitively charged.

A power control function may ensure proper function while optimizing the power consumption. It includes a start-up mechanism that controls the power delivery to the circuits in order to initiate the first measurement after a power-down phase, and may also include low power (sleep) settings to extend the device use. The system may include multiple power sources to extend the device use e.g. battery and inductive recharging of battery. The power control function will manage the multi power source configurations.

A feedback device may provide simple user information. This may be for example an light emitting diode (LED), piezo beeper or a mechanical vibrator/clicker that may be used to indicate whether a measurement has been completed successfully or whether an error has occurred. In addition, an alert/feedback mechanism may be employed in those situations where critical threshold parameters, e.g. temperature, are exceeded. This alert/feedback system would use the display (if present) and the feedback device (if present).

The CCM also may in certain circumstances contain a means of displaying the data being transmitted, e.g. a flexible or rigid visible display such as a liquid crystal display (LCD), organic light emitting diode display (OLED), magnetically reactive polymer displays (e.g. electronic ink), passive or active colorimetric or color based alert displays. The display unit may be mounted onto the CCM. Alternatively, the CCM may mount a simple audio alarm or alert.

Data Collection Unit (DCU)

The Data Collection Unit (FIG. **13**) may interrogate the CCM and receive a signal from one or more CCM's. The DCU may convert the received signal into a form that can be processed by the DCU control system e.g. a microcontroller. The DCU is intended to have more extensive means for data processing than the CCM. As a result, this may allow more complex signal processing and analysis. This function may improve the analysis of signals received and may enable management of data received from other applications. The results may be transmitted to a remote database management system through a communications network, e.g. a cellular phone network or the Internet. With this method, the data may be remotely collected, analyzed and summarized. The processed data may then be provided to other persons, e.g. a measured subject, clinician (physician), or authorized third parties. The receiving party may also communicate back to the measured subject or other authorized third party using the same communication network. This may enable the measured subject and clinician to remotely communicate diagnostic knowledge and/or actions resulting from review of processed data.

The utility of the device requires that the DCU have several attributes. These include, but are not limited to: the ability to transmit to and to receive data streams from the CCM, to communicate these data to secondary sites of analysis using such means as linkages through internet communication-based systems, cell phone-based communication devices, personal alpha-numeric paging networks or hardwired direct communication systems configured to receive and analyze such data streams. In addition, the DCU may also have a user input device, e.g. a keyboard, touch screen, as well as a display or actuators, e.g. a beeper, to serve as a user interface. A power supply for the DCU may be mobile, e.g. a rechargeable battery or it may be wire-bound, such as might be the case in wall mounted DCU units.

As such, one form of the DCU may be an accessory module placed within or otherwise connected to preexisting communication devices such as hand held cellular telephones and PDAs.

As the signal transmitted to the DCU may be weak, the DCU might be directly connected by wire or other means directly to the CCM. Alternatively, the DCU might be physically separate from the CCM and receive the signal by such means, but not limited to, electrical, photonic or mechanical (e.g. acoustical) generated signals. The HG system as a whole collects more data and measurements over time, which improves the diagnostic knowledge on the mammalian subject.

The remote database management system will store, analyze and summarized the collected data in a real-time environment. Custom algorithms and neural analysis will be used to interpret the collected data, with measured subject or clinician controlled customizable variables. This analysis will be summarized and either made available to the measured subject and/or clinician automatically by either posting the data in a system which would display e.g. Web based portal, or transmit the summarized data to the clinician and/or measured subject, this transmission may be a through a wireless communication system, a land based system e.g. phone call or facsimile, or printed and delivered to the physical location e.g. U.S. Mail, or other mail delivery system.

The data may be transferred from the DCU into a data management system which may further analyze the collected and transmitted signals/data. One of the advantages of the HG system with its continual monitoring allows the establishment of individual baseline measured bioparameters as well as inclusion in and comparison to a larger

bioinformatics database. This may facilitate identification of individual deviations or anomalies, as well as discerning population trends. This contrasts with current methods having transient or periodic measurements taken of an individual, e.g. once a day/week, which are less likely to detect deviations or anomalies.

Data Transceiving

For both the connections between BIH and CCM as well as between CCM and DCU, transmission protocols define how the data is transmitted (FIGS. **11–13**). They assure compatibility of different BIH, CCM and DCU models and high system reliability. The transmission protocols may vary in complexity depending on the application. For example, a preferred embodiment in the case of a wire-bonded BIH-CCM link, would be a transmission protocol as an analog resistance signal that is read in defined intervals. If a wireless transmission is used, the transmission protocols will be much more complex. Another factor that has an influence on the transmission protocols is whether the transmission is unidirectional or bidirectional. Bidirectional transmissions allow certain features like electronic handshaking, but require more hardware and energy resources.

A protocol definition includes the physical characteristics of the data connection (e.g. RF or infrared radiation, frequency, modulation types). Further, the data transfer mechanism may be specified. This may include synchronization and handshake mechanisms as well as repetition rates. The data structures of the protocol may define the amount of data that can be transferred. Typically the data is organized in blocks or packets that are sent repeatedly at specified intervals. As an example, a protocol may define a transmission block consisting of synchronization bits, an address field that contains ID information, a data field containing the data generated by the CCM from the BIH input and a checksum field allowing testing for data integrity at the receiver's end. The length of the data block variable may vary. This will be useful in minimizing power consumption and maximizing device lifetime.

For two-way transmissions, an electronic handshake is possible where the receiver indicates the successful reception of data. If the handshake signal indicates that the data was not received correctly the sender unit may retransmit. If there is only one-way transmission of the signal, it may be helpful to transmit the data signal more than one time in order to increase the likelihood of signal reception.

If a system is designed to have multiple devices sending data to one or more receivers using one-way transmission, it may be advantageous to use different repetition frequencies for the sending devices. Thus it may become more likely that sending devices do not interfere with each other. This problem may not occur with two-way transmissions since the sending device transmits by request only.

Either custom or available protocols (e.g. GSM, Bluetooth or IP) may be used depending upon the application, devices, environmental conditions (e.g. high noise or signal interference) and transmission requirements.

Based upon the above considerations and those in previous sections, a preferred embodiment for wireless communication between the CCM and DCU would be by RF using a frequency hopping spread-spectrum signal employing wireless medical band frequencies, e.g. between 609 to 613 or 1390 to 1395 MHz. The means to communicate would be two-way, employing electronic handshaking between the sender and receiver. The communication protocol would consist of information packets comprised of four sections: a header section; an 64 bit address section (therefore having 2^{64} possible numeric combinations for the device identification); an encrypted data section (encrypted using an algorithm based upon the address section ID); and a checksum or error correction section.

A preferred embodiment for wireless communication between a BIH assembly and a CCM assembly would be similar to the above preferred embodiment describing communication between a CCM and DCU unit. Conversely, data exchange between a DCU and higher level systems would employ existing communication protocols especially with regards to data encryption. In this case, a preferred means of encryption would be existing 128 bit TCP/IP based encryption at the SSL layer of signal transmission.

EXAMPLES

Uses and Applications of the HG include uses involving the measurement of physiological parameters, including but not limited to, temperature, blood pressure, heart rate, respiration, electrical measurements (e.g. EKG or ECG), pH, CO_2, pO_2, biochemical substrates (e.g. glucose oxidase, phosphatase, vitamins, nutraceuticals, hormone levels, etc.), radiation and magnetic spin states. The parameters may be useful indicators of physiological events, such as ovulation, or indicate abnormal physiological events, such as microbial infection, heart attack or diabetic shock.

Although the examples below are indicative of the type of uses the HG system can be applied to, they are not meant to limit the scope of the invention. Those of ordinary skill in the art can appreciate the many applications that the HG system could be used in, and with no undue experimentation, different sensors can be used to adapt to the application needed for each occasion.

Use of the HG to Monitor Temperature Changes in Patients

FIG. **14** depicts a HG configured to measure temperature changes either at the surface of the epidermal layer or subsurface in the dermal layer. For temperature measurements at the surface, the CCM **204** and BIH **202** are integrated into one single unit, where the BIH is in direct communication with the CCM. A power source **208** and transmitter **210** are included, where all components are mounted on a suitable substrate **212**, and attached to the mammalian subject using an adhesive patch **214**. The BIH contains sensors **206** that measure temperature changes, and can consist of one of many types of temperature sensors. A preferred embodiment of surface temperature sensors are thermistors, which are miniaturized, semiconductor-based devices capable of high sensitivity and resistance to extreme environmental conditions. Thermistors are readily commercially available (e.g. Precision Engineering, RTI Electronics, Inc., Wuntronic, Inc. and other manufacturers of NTC and PTC Thermistors), and can be custom fitted to many different applications. Temperature sensors can be placed on outer body surfaces, including the thorax, armpit, extremities and other body surfaces, as well as within cavities, such as the nasopharynx airway, oral cavity and in the ear canal in close proximity to the tympanic membrane (Exacon, Inc., D-TM1 sensor). Other examples of suitable temperature sensors include metallic wire (such as platinum) resistive temperature sensors, thermocouples, semi-conductor p/n junctions as well as other silicon-based diode temperature sensors and band-gap based sensors. Temperature sensitive materials, such as liquid crystals, may also be utilized which have a detectable change in physical properties that is proportional to a change in temperature. Alternatively, temperature sensors may consist of microneedles or other materials pen-

etrating the dermis to more accurately measure the measured subject's temperature (Exacon, Inc. DN1205 and DF1350A). The temperature in this case would be measured by either thermistors or other gauges within the needles, etc. or by conducting the internal temperature back to the surface by heat conductive materials, e.g. conductive metals or organic materials with high heat transference. Changes in the temperature sensor **206** are automatically communicated to the CCM **204**, which automatically relays the data stream to a remote DCU unit located either on the person, or to a collection station nearby.

An example of the utility of a temperature sensor incorporated into a continuously monitoring HG system is seen for monitoring of an ovulation event. Detectable physiological changes, such as temperature, occur when the egg is released from the ovary into the fimbrae of the fallopian tubes and eventually into the uterus. Fertilization of the ovulated egg must occur within a narrow window (24 hours) of the ovulation event, making timing of sexual intercourse essential for a successful fertilization event. Although detectable, the temperature changes are minute relative to basal body temperature. Therefore, establishment of an accurate baseline temperature is critical for successful prediction of ovulation. Since basal body temperature is circadian in nature, this requires repeated temperature monitoring throughout the day in order to get accurate baseline values. The HG will continuously collect data and establish accurate baseline values for a given time period. A rise in temperature as compared to the baseline values indicates onset of ovulation. Upon that detected rise, the data collection unit will alert the patient through various communication systems, including but not limited to a remote paging system, telecommunications pathway, e-mail or other internet linkage, voice-mail linkage, through the patient's care provider or other types of communications pathways.

In order to obtain repeatable core temperature readings, it is important to select an appropriate site for placing the sensor system. One such location would be an intrauterine or vaginal placement of the device. In this situation, the BIH/CCM assembly may be packaged in the form a biocompatible capsule or other non-irritating shape and would adhere to the surface either through mechanical, e.g. adhesives, microfilaments or hooks, or be held by physical placement, e.g. as a part of a larger loop or inserted device. In such a form, the BIH may mount additional sensors beyond those of temperature, including sensors to detect cyclic hormones, e.g. luteinizing hormone, follicle stimulating hormone, progesterone, estrogen, or their metabolites, or other biomolecules passed into the reproductive tract that would serve as indicators of follicular status.

In general, monitoring temperature changes is important for other physiological conditions, including the early indication of short term infectious states (general increase in temperature) a sign of shock (general decrease in temperature), non-compliance with therapeutic regime causing localized temperature shift (diabetes, hypertension), or long term deviations or shifts in temperature which are indicators of illness (arterial sclerosis) that are not easily detected with current diagnostic methods. In addition, monitoring temperature is routine in studies or situations where monitoring of patient vital signs is necessary, such as in premature infants, infants, daycare children, geriatric patients or hospital situations.

Veterinary Applications of the HG for Monitoring Temperature Changes

Monitoring temperature changes is not only important for humans, but also in the veterinary field. An increased temperature is a general indicator of infection, and may be an important early indicator to stop the spread of an infectious disease. One such agent responsible for decreased production of milk in dairy cattle is *Pasturella hemolytica*. The information from a device that can detect changes in temperature can be relayed to a data collection unit. The data is analyzed, allowing a farmer to identify the individual through a unique ID assigned to the BIH/CCM device attached to the animal, and isolate the contagious animal before it spreads through the herd. Depending on the size of the animal, the device need not be miniaturized, circumventing the need for extensive engineering. The device could also monitor other bioparameters, e.g. including those relating to general health, reproductive status, nutritional status or activity.

Other veterinary applications include the use of the device in monitoring laboratory animals during experimental manipulations in order to simplify the measurement of important physiological parameters, which indicate the efficacy or non-efficacy of pharmaceutical or other types of treatments. For example, laboratory rats may be equipped with a BIH/CCM assembly and monitored in a continuous or periodic fashion for vital signs, such as temperature, respiration, heart rate and other physiological parameters. BIH/CCM assemblies from several laboratory rats may be transmitted to one DCU. The amount of BIH/CCM assemblies transmitting to one DCU may be limitless because of the encryption and data identification transmission, as well as handshaking, protocols which will be employed. The DCU may then transmit data from the plurality of BIH/CCM assemblies to a remote database management system for further analysis and summarization of the data. This may potentially streamline the data gathering process, allowing more experiments to be conducted in a shorter period of time with no animal handling necessary.

Use of the HG to Monitor Physiological Parameters at the Surface of the Skin

Additional physiological parameters could be measured using the above technology at the surface by replacing the temperature sensor device with another application appropriate sensor. Examples of this include heart rate (pressure detector, strain gage, optical surface tension, electrical output or other technologies), respiration (pressure detector, optical surface tension, strain gage, electrical output or other technology), electrocardiogram measurement (Ag/AgCl electrodes; other technologies), surface pH (some type of electrode), oxygen consumption (Clark electrode, partial pressure of O_2, luminescent quenching) and other physiological parameters. Other surface monitors include sensing chemical and biological elements such as non-invasive glucose monitoring through the skin for diabetic patients.

Use of the HG for Vital Sign Monitoring in Patients

In addition to monitoring a single physiological parameter, multiple sensors could be incorporated onto the same BIH to allow multiple parameters to be measured simultaneously. These multiple parameters may be measured by using one or more BIH assemblys that would contain one or more sensors, appropriate to the application, e.g. pressure sensor to determine HR and micro-cantilever to sense potassium discharge through the skin, measuring and communicating the collected values to the CCM, which would filter and combine the data and transmit to the DCU. The DCU

would then complete the signal processing and interpret (calculate) the signals into the appropriate application specific format e.g. Heart Rate, or use this data to then project or estimate a health parameter that is highly correlated to the measured value, e.g. daily calorie consumption. This would enable the continuous monitoring of the measured subjects vital signs, e.g. heart rate, respiration rate, potassium discharge in both a hospital setting, as well as in ambulatory use. An example of a use of the HG in vital sign monitoring is found for infants that may be predisposed to Sudden Infant Death Syndrome (SIDS) premature infants could be fitted with one or more BIH/CCM assemblies which would include sensors that monitor blood pressure, respiration, oxygen consumption, heart rate, ECG and temperature. The unit is miniaturized to decrease risk of removal or rejection by patient, as well as to decrease the surface area variability that may pose a problem for smaller patients. In addition, the unit is thermally insulated to decrease the effects of volatile ambient environmental temperatures, such as those found in an incubator, may have on patient temperature. The sensors on the BIH can either be in direct communication with the CCM, or can communicate with the CCM wirelessly, such as through radio frequency or other means of telemetry. Wireless connection of the CCM with the BIH may prove advantageous for sensors that require multiple locations to accurately determine physiological value. The CCM transmits the data stream generated by the multiple sensors on the BIH to the DCU. The DCU can collect sufficient data points to generate reliable current values, and also monitor the patients condition such that upon triggering a pre-determined value, the uploading of information by the DCU into the remote data analysis system enables the clinician to be alerted if a measured parameter moves outside a preset range. This clinician alert can be provided through existing telecommunication systems or with the wireless data communication system with in the HG.

An alternative use of the multiple sensors system would be to monitor multiple parameters that when combined are statistically correlated to either an illness or health maintenance factor. One such embodiment is the use of temperature, heart rate, respiration rate and potassium discharge through the dermis in order to obtain an assessment of kilo-calorie expenditure. This is envisioned as a method to better manage overall health with a measurement of energy expenditure to that diet and weight may be more precisely coordinated. Temperature sensors include thermistors, metallic wire (such as platinum) resistive temperature sensors, thermocouples, semi-conductor p/n junctions as well as other silicon-based diode temperature sensors and band-gap based sensors. Respiration rate may be monitored by chest cavity distension and employ sensors such as strain gauges, including those based on Wheatstone Bridge resistance change measurements, pressure transducers or bands worn around the chest coupled with strain gauges to evaluate chest expansion. Suitable ion specific microelectrodes or related sensor devices may measure potassium discharge. When combined, a profile of these measurements indicate energy consumption and coupled with other patient specific parameters such as weight, would describe kilo-calorie consumption.

Use of the HG for non-invasive Blood Pressure Monitoring in Patients

In addition to monitoring a multiple parameters on a single BIH, various types of physiological parameters may be determined indirectly (correlated) or calculated from values obtained from a plurality of non-invasive or invasive BIH/CCM assemblies located on the measured subject, and using preset variables such as distance, time or location in the calculation/correlation of the parameter.

An example of a multiple non-invasive BIH/CCM application would be the calculation of blood pressure. The blood pressure would be calculated by the DCU using measurement data acquired from two or more BIH/CCM assemblies with one or more of the sensors previously noted to measure the physiological parameter (i.e. heart rate can be measured with a pressure transducer sensor). This non-invasive system is of particular value to clinicians and patients today because of a prevalent condition called the "White Coat" effect. This condition is experienced by many patients today due to anxiety associated with being at their clinician's facility, causing their heart rate and blood pressure to be elevated while in the clinician's facility. As a result, many patients are either misdiagnosed with hypertension or required to return to the care providers facility numerous times to validate the clinicians diagnosis. By enabling clinicians to remotely, automatically and continuously monitor the patients blood pressure they would be enabled to better diagnosis the presence of hypertension and accordingly take the necessary diagnostic actions.

Blood pressure can be calculated in the DCU by locating two BIH/CCM assemblies on the measured subject at a set distance or location. By locating at least two devices on the measure subject, separated at a specified distance, then measuring the heart rate (diastole) from both BIH/CCM devices, then transmitting this data and a time reference for each of the measured values to the DCU. Then inputting into the DCU other relevant variables of the measured subject the Blood Pressure could be calculated. Those inputted values could include the measured subjects gender, weight, height, age, and ethnicity.

In addition to providing the blood pressure values this application would also enable clinicians and patients to monitor patients compliance to therapies prescribed or recommended by the clinician. By enabling either direct measurement or calculation of parameters in a remote continuous environment changes in behavior and/or compliance can be detected. Hypertension is typically treated with a therapeutic medication that must be taken by the patient at clinician prescribed intervals e.g. every 8 hours, if the patient does not take the medication the illness may reappear i.e. blood pressure rises. This application of he technology would enable the detection of non-compliance and reminder to take their medication. The feature of the HG as a compliance monitor is applicable to most of the applications envisaged including both the non-invasive and invasive applications.

Use of the HG to Monitor Blood Parameters in Patients

A HG may be configured to measure various physiological parameters of blood. An invasive BIH assembly is implanted into the patient consisting of sensors that monitor oxygen levels, carbon dioxide, pressure, pH and other physiological parameters important in assessing patient health and condition. The BIH assembly may itself consist of a needle, designed to self-insert into a vascularized compartment, such as a blood vessel. The BIH assembly may also be inserted into the patient with the aid of a surgical instrument that makes a small incision and guides the BIH assembly into the patient, such as a trocar or other surgical instrument. In addition, surgical implantation techniques will be used for implants that are deeply embedded (i.e. below the hypoder-

mis/subcutaneous layer) into the patient host. It is essential that all implantable devices be sterilized prior to insertion into the patient.

The BIH assembly may comprise a flushing system, designed to decrease trauma and adherence of the BIH assembly onto surrounding tissue. This biofluidics system would contain physiological solutions, such as saline, and may also contain antibiotics, antifungal, antimicrobials, or other compounds designed to inhibit the growth of infection-causing organisms. The biofluidics system may also contain anti-inflammatory agents as well as other agents to locally suppress the immune system surrounding the BIH assembly to decrease rejection incidence and increase the longevity of the sensor unit.

After insertion of the BIH assembly, the assembly is adhered onto the skin with specialized adhesive biocompatible materials (transdermal patch) that allow ventilation of the transdermal conduit while maintaining sterility of the assembly. The transdermal patch may be comprised of microporous nylon, thermoplastic microfibers, polypropylene, other polymers or other microporous films which form a barrier against extrinsic liquids, yet enable water vapors, i.e. perspiration and other bodily fluids, to flow freely through the fabric. The fabric should also insulate external conditions from influencing the function of the sensors, such as temperature, pressure, partial O_2 pressure and other physiological parameters affected by extreme environmental conditions. The BIH assembly may communicate directly with the CCM assembly through nylon tape, filaments or metal wire connections, or communicate wirelessly via RF or any other telemetry technology, continuously transmitting data from the BIH sensors to the DCU. In order to decrease the risk of occlusion of the sensors or accretion of biological materials onto the sensors that would hamper performance, the biofluidics system may automatically flush the biosampling access point area upon detection of build-up or adherence of material onto the sensor head or at defined time intervals. Alternatively, the region may be flushed either manually or upon replacement of the biosensor component. The detection of biological material build-up may be through sensors which sense changes in pressure or optical clarity of the environment immediately surrounding the sensors or by any other means that can detect accretion of biological materials that would hamper sensing ability. The transdermal conduit incision area may also be manually flushed periodically to decrease adherence of biological materials on the sensor itself.

Data collection and analysis of signal output from the implanted BIH sensors will depend upon the implantation depth of the sensors. Subcutaneous implants could either transmit data to the CCM directly through nylon tape, filaments or insulated metal wire connections, or communicate wirelessly via RF on any other telemetry technology. Implants that are below the subcutaneous layer and into underlying organs may require wireless telemetry for communication of sensor data to either the CCM or DCU. This wireless transmission may be electrical (RF) or acoustic.

Use of the HG to Measure Glucose, Fructosime and Hemoglobin lac levels in Patients

The HG may be configured for measuring glucose, fructosime and Hemoglobin lac levels in diabetic patients. Determining accurate levels of these three elements is crucial to achieve metabolic control of diabetic patients in order to avoid hypo or hyperglycemic situations. Specific knowledge of glucose levels allows diabetics to self-regulate exercise, diet and insulin regimens, a condition crucial to avoiding adverse clinical situations.

Traditional methods of monitoring glucose levels includes multiple blood sampling, through finger pricking or other means, and measurement of glucose levels through glucose oxidase/peroxidase colorimetric reaction.

Non-invasive methods of measuring glucose levels have been developed, including the use of reverse iontophoresis to measure glucose levels, the extraction of glucose from interstitial fluid and the use of infrared laser for measuring levels of glucose in fluids. Glucose sensor methods could be incorporated into the BIH assembly of the HG for continuous glucose monitoring. By doing this, more accurate baseline measurements could be obtained with automatic downloading of information from the different sensor systems. Pre-set sensor levels could alert the patient to hypo- or hyperglycemic levels through various telecommunication pathways, including a remote paging system, telecommunications pathway, e-mail or other internet linkage, voice-mail linkage, through the patient's care provider or other type of communications pathway.

More elaborate sensors could also be used which may provide more accurate measurements than currently achieved with non-invasive glucose monitoring systems. An implantable sensor with glucose oxidase at the tip of the BIH sensor would detect glucose through a colorimetric reaction, similar to what is obtained with current hand-held glucose monitors. In addition, other sensor systems, such as electrical detection, potentiometric detection, or any type of detection method could be used in conjunction with the BIH glucose sensing head. For example, deposition of glucose oxidase on self-assembled polypyrrole films would allow measurement of glucose levels through an electron-transfer reaction, allowing levels to be determined according to the relative conductivity of the film (Ram et al, 1999). Self-calibrating structures (microchannels, vesicles, microcompartments) could be incorporated into the silicon wafer microstructures, allowing automatic calibration of the sensor at set intervals throughout the day.

Use of the HG to Measure Drugs or Small Biomolecules

Drugs and other small biomolecules could be monitored using the above technology at the surface by replacing the invasive glucose sensor on the BIH with another appropriate sensor, depending upon the application. (This sensing may be also enabled with an application orally.) Drug monitoring is useful for comparing the efficacy of drug treatment regimens with levels of the compound in vivo in patients. Drug monitoring also overcomes potential polymorphic differences between individuals that could result in over- or underdosing of patients due to differences in drug metabolizing enzyme activities. Drug sensors used would include specific antibody-loaded sensors, enzymes specific in the metabolism of various drug compounds (cytochrome P-450 enzymes, etc.) and other technologies utilized in the detection and measurement of therapeutic pharmaceutical compounds. Sensors could also monitor drug tracers that pharmaceutical manufacturers routinely include in therapeutic formulations. Using tracers to monitor the presence of the prescription drug in the body may assist in determining compliance or effectiveness of therapies, as well as identifying possible counterfeit formulations that may be in use by the patient.

Sensors that monitor the presence of illicit drugs could also be incorporated into a BIH. Sensors important for this application include the monitoring of cocaine, heroin, marijuana, amphetamines and other illicit compounds that would

require monitoring on a regular basis. Any detection of illicit compounds in an individual would result in the automatic notification of the appropriate legal authorities. In addition, alcohol levels could be monitored by using pre-set levels determined by the laws of each state. Upon the elevation of alcohol levels beyond these pre-set levels, an alarm would be triggered whereby the appropriate authorities would be automatically notified. For both the detection of illicit compounds and illegal alcohol levels, a feedback loop would also automatically disengage motor vehicle operation, preventing the individual from operating any motor vehicle connected to any of the telecommunication systems listed above.

Use of the HG in Monitoring Serum Proteins and Microorganisms

The HG could also be configured to measure serum protein levels. For example, levels of atherogenic markers, such as high-density lipoprotein, low-density lipoprotein or lipoprotein-a may be measured with antibodies attached to the sensor head. The antibodies may be attached to microcantilever structures and detected through optical or potentiometric methods, as described in U.S. Pat. Nos. 5,445,008 and 6,016,686, incorporated herein by reference. Binding of the specific serum proteins to the antibodies may also be detected via colorimetric or electrochemical-mediated reactions. Other methods that are otherwise known to those of skill in the art are intended to be incorporated here by reference, and may be used in conjunction with the methods described here.

In addition to the measurement of serum lipoproteins in blood, microorganisms, such as Salmonella, *E. coli*, Streptococci, Chlamydia sp. (including *C. trachomatis* and *C. pneumoniae*), Pseudomonas, the HIV virus and other microorganisms, may be detected through antibody, enzyme-mediated detection sensors or any other microorganism detection technology. Of high importance is the monitoring of nosocomial infections in hospital situations. A BIH sensor head may be configured to contain not only vital sign measurement, but also detection of infectious organisms in patient samples. The sensor could be placed in an implantable platform, as above, but also in needles, catheters, respiratory implants or any other implants used in a hospital setting. The sensor could be queried using telemetry technology to continuously monitor the presence of infectious organisms, or directly linked to the BIR through electrical conduction means. The BIH could also be placed in devices or equipment adjacent to the patient for detection of the types of materials being inserted/injected into the patient e.g. Intravenous Pumps and Mechanisms, Respiratory devices, kidney dialysis systems, blood sampling systems and devices, fluid discharge containment devices e.g. bed pans, urine samples, sputum samples, oral sampling devices and systems e.g. cotton swabs, tongue depressors, nasal secretion collection devices e.g. bulbs etc.

The BIH sensor, through a uterine or vaginal implantation device, could also measure the occurrence of uterine or vaginal infections, such as yeast (fungal) infections, Human Papilloma virus, Epstein Barr virus, sexually transmitted agents, or other uterine or vaginal infection. For example, yeast infections could be monitored through the specific detection of agents, such as *Candida albicans*, by antibody-mediated detection, enzyme detection, or other means routinely used in detecting Candida infections. In addition, a second sensor monitoring pH levels may also be incorporated. pH levels are indicative of ideal environments for Candida growth, where a decrease in the acidity of the vaginal environment releases growth inhibition of Candida, and transforms the microbe from a yeast-like to an invasive fungal mycellium form. Early detection of changes in physiological parameters or presence of microbial agents is essential in the prevention and treatment of disease states, including Chronic Fatigue Syndrome.

Use of the HG for Oral Measurements

The mouth is a less commonly employed site of bioparameter measurements but offers a number of significant advantages, including the ability to access body fluids and to monitor exhaled gases. In certain instances, these may serve as alternative measurements to invasive techniques. Using suitable sensors, e.g. a microcantilever MEMS systems, it is possible to measure ketone or aldehyde content within saliva and therefore gauge dietary/nutritional status (e.g. catabolic dietary deficiency) or, for the purpose of breath acceptability in social settings. In other applications, exposure to chemical or biological warfare agents may be assessed by placing within the buccal cavity suitable sensor systems e.g. those for volumetric measurements of oxygen consumption (or partial pressure of oxygen gas, or other gases such as cyanide, Lewisite, or specific toxins or agents. In addition, an oral device could be used to ensure compliance to a therapeutic regimen by analyzing the exhaled gases or fluids within the mouth for markers or other chemical or biological elements that would correlate to the concentration of the therapeutic in the measured subject.

In use, a BIH/CCM system may be affixed to the outside surface of the teeth. Alternatively, a combined BIH/CCM may be placed or positioned between teeth and held in place by dental floss or other similar type device.

Use of the HG for Measurement of Other Biological Parameters

Measurement of other biological parameters that were not contemplated in the preceding examples may be accomplished using the above system by incorporating the appropriate sensor into the HG. For instance, it may be readily envisaged how one skilled in the art might utilize a HG system to augment hearing in select circumstances by placing an acoustic sensor/transmitter BIH assembly within the ear as a cochlear implant and utilize the CCM to transmit data representing audible sounds to the ear. In addition, it will be understood that the present invention may be implemented using other technologies, including direct digital readout of signal output from the sensor platform, and other technologies known to those of skill in the art. All such variations and modifications are intended to be within the scope of the invention claimed by this patent.

We claim:

1. A system for monitoring physiological status of a mammalian subject, comprising:

a. one or more biointerface heads (BIH), each comprising one or both of a sensor for measuring a physiological parameter and a device for therapeutic compound delivery, at least one of said biointerface heads being implanted subdermally and configured to communicate data and a BIH identifier;

b. at least one control and communication module (CCM) attached to an external surface of said subject and storing a CCM identifier and which is linked to at least one biointerface head to receive said data and said BIH identifier, wherein said control and communication module processes data from at least one biointerface head;

c. at least one data collection unit (DCU) which receives data and said identifiers from the control and communication module; and

d. a remote database management system which receives data from the at least one data collection unit and processes said data.

2. The system of claim **1**, wherein said biointerface head is attached to said mammalian subject with at least one adhesive.

3. The system of claim **2**, wherein said adhesive contains one or more of the groups comprising: growth factors, adherence molecules, adherence attractants or factors which promote cutaneous wound-healing mechanisms and formation of an epithelial-like structure around a portion of said system.

4. The system of claim **1**, wherein said system comprises a transdermal conduit and a biofluid access port, and wherein the transdermal conduit and biofluid access port are coated with a hydrogel material.

5. The system of claims **4**, wherein the hycirogel material contains preservatives, anti-inflammatory agents, antibiotics or antimicrobial agents.

6. The system of claims **4**, wherein the hydrogel material contains a chemical, compound or molecule for calibration of the sensor.

7. The system of claim **4**, wherein the transdermal conduit comprises a fluid material containing preservatives, anti-inflammatory agents, antibiotics or antimicrobial agents.

8. The system of claim **1**, wherein said system comprises a chamber which releases one or more therapeutic agents.

9. A system comprising:

a subdermal physiological parameter sensor to measure a physiological parameter of a mammalian subject and to generate measurement information based on the measurements;

a mounting structure that anchors said system to a dermal layer;

a flexible transdermal conduit attached to said mounting structure at or near a first end, wherein said transdermal conduit is in contact with a sensor assembly;

a sensor mounting head, wherein said sensor mounting head is attached to a second end of said transdermal conduit;

a biofluid access port within said sensor mounting head, the biofluid access port further comprising microstructures allowing biofluid flow into the transdermal conduit to contact the sensor assembly and block transmission of external pathogens into a subject;

a control and communication module in data communication with the physiological parameter sensor to receive the measurement information from the physiological parameter sensor, the control and communication module including signal processing circuitry to generate and transmit a first signal based on the measurement information.

10. The system of claim **9**, wherein the control and communication module further comprises signal encryption circuitry to encrypt the first signal for transmission.

11. The system of claim **9**, wherein said mounting structure is attached to said mammalian subject with at least one adhesive.

12. The system of claim **11**, wherein said adhesive contains one or more of the groups comprising: growth factors, adherence molecules, adherence attractants or factors which promote cutaneous wound-healing mechanisms and formation of an epithelial-like structure around the mounting structure.

* * * * *

Fiber optic biosensor using phase tracking

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Inventor: CHEN DUAN-JUN (US)
Applicant: BIOFIBER INDETIFICATION INC (US)
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Abstract of **TW558635B**

The present invention discloses a fiber optic biosensor using phase tracking to detect the existence and degree of variation of some specific biological (or chemical) material. The biological probe of the sensor uses fiber as the substrate, the tip of the fiber is coated with one or more layers of materials different from that of the fiber and the tested material, which can be the sensing standard of the thin-film reflection interferometer, wherein at least one layer is the compensated material which can absorb the target biological (or chemical) molecules to be tested. When the molecules to be tested are absorbed on the surface or interior of the complementary material, the spectrum distribution of the reflection/interference light will vary. The spectral line shift is for analyzing quantitatively or qualitatively the concentration, adhesion rate and geometrical size of the sample molecules.

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	英文	
二、發明創作人	姓名	陳端軍
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裝 訂 線

四、中文發明摘要（發明之名稱：應用相位追蹤的光纖生物檢測儀）

本發明係揭示一種用於偵測某種特殊生物（或化學）物質之存在和變化程度的一種應用相位追踪法的光纖生物檢測儀。該檢測儀的生物探針是利用光纖作爲基質，光纖的頂端首先塗有一層或多層與光纖和待測物質不同的材料，可以作爲薄膜反射干涉儀的感測標準，其中至少一層是能吸附待測目標生物(或化學)分子的互補材料。當待測分子吸附到互補材料表面或內部以後，將會改變反射干涉光的光譜分布。這種譜線偏移即用來定量或定性地分析樣本分子的濃度、附著速率、以及幾何尺寸的變化。

英文發明摘要（發明之名稱：）

五、發明說明（　）

發明領域

本發明係涉及光電檢測技術領域的一種檢測裝置，更進一步係涉及用於檢測某種特殊生物（或化學）物質之存在和變化的一種應用相位追踪法的光纖生物檢測儀。該檢測儀利用光纖作爲基片的生物探針，塗在探針上的生物和化學塗層（直接塗上或者經過處理的）可以作爲薄膜反射干涉儀的感知基準，其中至少一層是能吸附待測目標生物(或化學)分子的互補材料。在待測分子吸附到互補材料表面或內部以後將會改變反射干涉光的光譜分布。這種譜線偏移即用來定量或定性地分析樣本分子的濃度、附著速率、以及幾何尺寸的變化。

發明背景

檢測樣本中是否存在某種特殊的生物或化學物質，是在生命科學研究、藥品開發和醫學診斷中經常用到的方法。例如，在免疫檢測中，需要檢查血漿中是否存在某種特殊的抗體。抗原是一種能夠與其互補抗體發生反應的物質，因此可以用它來檢查血漿中其互補抗體是否存在。生物檢測可以用擴散法、電泳法、螢光法等方法來檢測某種抗體是否存在，以下將對每種方法進行簡單說明。

免疫擴散法(immunodiffusion)一般係用於免疫測試。它是一種血清的處理過程，抗體和抗原溶液通過細胞凝膠層互相之間擴散。抗原和與之互補抗體之間的作用表現爲兩種液體之間的一條沈澱線。

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電泳法(immuno-eletrophoresis)係廣泛用於多種生物檢測。它也是一種樣本的處理過程，利用電泳所產生的離子移動將被測成分分離出來，再通過其互補生物體的擴散或標記作用來觀察它們。螢光法(Immunoflorescence)是一種識別生物反應的過程，某種抗原附著於特殊標記上，被某種波長的光（例如紫外光）照射時產生螢光，由此可以很方便地識別這種抗原。其他的標記還有放射性同位素、電子、磁性和酶標記等。

用光纖測試最普遍的方法係為以螢光法來識別生物物質之光纖螢光和化學冷光(chemi-luminescent)生物感應器。這種光纖感應器係爲商品化應用和研究開發中應用最廣泛的一種。有兩種類型的光纖生物感應器係被用到：夾層生物感應器以及位移生物感應器，其係分別經由不同作用方式所作動。關於夾層光纖生物感應器和位移生物感應器的使用係分別被說明在圖1a、圖1b、圖1c、和圖1d中。爲方便起見，吾人係以抗原抗體的測試爲例來說明各種生物感應器的工作原理。

如圖1a所示，夾層光纖生物感應器係依下列方式所產生：將末端塗有試劑102（如抗原）的光纖100浸入溶液104，來檢測溶液104裏是否存在與試劑102互補的抗體106。若溶液104中確實存在互補抗體106，則該抗體係與試劑102相結合。光纖100要在溶液104中浸足夠長的時間，以保證足夠長的反應時間，然後用諸如鹽水之類進行洗滌。

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如圖1b所示，將塗有試劑102的光纖100以及結合於其上的抗體106浸入試劑110（如抗原）中。標號爲112的物質(如螢光指示劑)係被試劑110所吸附。當抗體106與試劑102結合時，帶有標誌112的試劑110係會與抗體106相結合。如此，光纖100係得為其根部的光源（在圖示中並未顯示）所照亮。在光纖100的末端，先是與試劑102結合的抗體106，然後是與抗體106結合的帶有螢光標誌的試劑110。試劑110係被光照所激勵。返回一個螢光信號。最終光纖生物感應器上會有：試劑102、抗體106、帶有標誌的試劑110排在最後，故稱之為夾層光纖生物感應器。針對夾層光纖生物感應器而言，在測試樣本中抗體106的濃度越高，就會有更多的帶有螢光標誌的試劑110與其結合，因此返回的螢光信號越强。

如圖1c所示，位移光纖生物感應器係為由光纖100及其末端所塗試劑120（如某種抗原）所組成。帶有酶標記124的試劑122（抗體）被密封在一個有透析能力的薄膜130裏。試劑122（抗體）與試劑層120（抗原）互補。因此，試劑122總有與試劑層相結合的傾向。將這套裝置浸入樣本溶液150中，檢查樣本溶液150裏是否有也與試劑120互補的抗體140。如圖1d所示，如果樣本溶液150裏含有該抗體，此抗體就有與帶有螢光標誌的試劑122競爭，與光纖100末端抗原層120結合的傾向。這時，在光纖100的根部加上光源（在圖示中並未顯示），與試劑層120結合而帶有標誌的試劑122受到光的激勵，返回一個螢光信號。在這種情況下，在樣本溶液150中抗體140濃度越高，

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在光纖100的末端就會有更多的帶有標誌的試劑122離開與之相結合的試劑120，結果返回的螢光信號强度越弱。所以，抗體140的濃度係與返回的光强成反比。

以上所述之光纖生物感應器係具有不少缺點。就夾層光纖生物感應器而言，光纖100要先浸入樣本溶液104，清洗，再浸入含有試劑110（帶有標誌112）的溶液108中。化驗需經過兩個不同的反應步驟，較爲麻煩。而且，只有當待測物的濃度高於某個臨界值之時方得被檢測出來。抗體106與試劑102結合的速率並無法即時(real time)測定。再者，由於化驗麻煩，以及大多數標誌（如螢光指示劑）為有毒者，夾層光纖生物感應器係無法用於體內進行直接檢測。

大多數標誌存儲時並不穩定，尤其是在光照下。另外，上述方法中的光强信號易受環境和系統包括雜訊的影響，如光源不穩，溫度變化，纖維彎曲引起光損耗等。

針對位移光纖生物感應器而言，薄膜130係增加了生物感應器的成本和尺寸。由於這種感應器體積較大，試劑的標誌可能有毒性，因此亦不適用於體內檢測。

另一種類型的光學感應器稱之為表面電漿子共振（Surface Plasma Resonance或簡稱“SPR”）感應器，如圖2a所示，其係包括有一個鍍有很薄金屬層204的棱鏡202，金屬層204係成爲棱鏡與絕緣體208之間的界面。一束橫向的磁化單向偏振光(magnetically polarized monochromatic light)入射到棱鏡202的一面，被金屬層204反射，而到達棱鏡的另一面。反射光束

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的強度係可以測量出來，用以計算入射光束206的入射角θ的大小。如圖2b所示，折射光束的強度在某一特殊入射角θSP處突然下降，在這個特定的角度下，金屬和絕緣體交界面激發所產生的表面電漿子（Surface Plasma或"SP"）波將與入射光的能量相互共振。如果一層薄膜沈澱在薄金屬層204上，絕緣物質的有效折射係數會發生改變，尤其是金屬層附近。有效折射係數與絕緣物質和沈澱膜的厚度和密度的大小有關。因此，如果沈澱膜的厚度發生變化，折射率就會改變，而臨界入射角θSP也會改變。藉由測量臨界入射角θSP的值，沈澱膜的厚度和密度就可以推導出來。

針對光纖型SPR感應器而言，其檢測信號的方式與幾何光學的SPR感應器相似。除了單色光源之外，波長在一定範圍內的多色光源也可以用來照明。在此，光學耦合效率係隨波長不同而改變。在某一特定波長處，反射光的光強達到一個極小值。另外，沈澱膜的厚度和密度發生改變，反射光強極小值處的光波波長從一個值變爲另一個值。這樣，追踪反射強度最小值處的波長移動，纖維圓柱表面上沈澱膜的厚度和密度就能測定。

R. C. Jorgenson等人在其文章"A Novel Surface Plasmon Resonance Based Fiber Optic Sensor Applied to Biochemical Sensing"中討論一種可以測量蛋白質濃度的SPR光纖感應器。該文發表於Fiber Optic Sensors in Medical Diagnostics, SPIE Vol. 1886, pp 35-48 (1993)。圖2c顯示了該文中提出的SPR感應器

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包括一多膜光纖210。其中一段光纖的外層被切除，留下的光纖芯線塗上了金屬薄膜，如銀等。

圖2d是一個探測器的示意圖，與圖2c相似。系統包括一個光源228，其係經由光纖234而與分光器(beam splitter)222相連。光源228是具有一定波長範圍的多色光。分光器222的輸出係經由連接器224和光纖238而與一個模式編碼器(mode scrambler)226相連。模式編碼器226係與探測器光纖的芯線210和外殼212相連，而該光纖係浸入到液體樣本216中。一個由光纖芯線210底端的3000A^{0}銀鏡218反射的信號係經由模式編碼器226、光纖238、連接器224和分光器222以及光纖236，而提供給攝譜儀(spectrograph)230。攝譜儀230係用於測量光強，而光強係為波長的函數。根據這些數據，550A^{0}銀層或金屬214上覆蓋薄膜的厚度就可以測出來。

雖然SPR感應器具有許多優勢，如它不需要標記，測量也可以連續進行，但是不足之處是在製造SPR感應器時，必須在切除光纖表層後，將很薄的高反射率的金屬層鍍在光纖內芯上，這增加了生產成本。此外，SPR感應器是一個相對較大的圓柱型表面，這樣較大的圓柱型表面積係需要較大容量的試劑和較多的測試樣本。同時，這類感應器的結構較難實現陣列式並行測試。另外，這樣的設計也無法用於體內檢測。

另一種類型的生物感應器係為光柵生物感應器。W. Lukosz 等人在題爲"Output Grating Couplers on Planar Optical Waveguides as Direct

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Immunosensors" Biosensors and Bioelectronics, Vol. 6, pp.227-232 (1991)的文章中描述了此類感應器。如圖3 所示，一束入射雷射束302係進入平面波導(planar waveguide)304的一端。平面波導304係包括一層非常薄的高折射率膜306，以及其上被設置有該膜之玻璃基質308。薄膜306的一部分表面係被設置有一光柵310。表面突起光柵310係使雷射302以α的角度射出平面波導，其中α是波導法線與光線的夾角。α的大小係與雷射之導向模式的有效折射係數有關。

表面浮雕光柵元件(surface relief grating)310係可以塗上一層試劑。可以用盛有液體樣本314的容器312運載表面浮雕光柵元件310。如果樣本314中的物質與試劑層發生反應，有效折射係數係會發生變化，從而改變反射角α。

透鏡316將出射光束聚焦到一個一元位置敏感成像檢測器(one-dimentional position sensitive photodetector)（或"PSD"）318。PSD318的輸出係藉由類比數位轉換器(analog-to-digital converter)320所採樣，並將結果送入個人電腦322中進行分析。經由有效折射率改變所引起反射光束角度α的變化係與試劑及其相結合之物質所生成的薄膜厚度有關。

光柵生物感應器有很多缺點。首先，感應器反應較遲鈍，即所謂"漂移效應(drift effect)"。如果測試樣本中含有被測物的濃度很低，就很難判斷有效折射率的的增加是否由漂移效應引起。第二，光柵生物感應器無法用於遠

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距離測量。另外，由於它的尺寸比較大，因次並不適合做體內檢測。這樣大的尺寸不利於對單一樣本做多次檢測。而且，感應器太長，需要較大量的檢測樣本。最後，製造內置光柵的平面波導較爲複雜且造價高，尤其是將製程微小化時。

另一種生物感應器係為以微管Fabry-Perot干涉(microcuvette-based Fabry-Perot interferometer)爲原理的生物感應器。在題爲“Direct Monitoring of Antigen Antibody Interactions by Spectral Interferometry,” Sensors and Actuators, Vol. 6, pp.96-100 (1992)的文章中，Brecht等介紹了一個例子。如圖5所示。由玻璃或石英製成的基底514上覆蓋一層聚苯乙烯膜502，如圖6所示，基底514和膜502放置於流動槽602的底部，用矽做槽頂。分叉多股石英光纖604連接到基底514上。604 的第一個分支606與光譜攝製儀610相連。另一分支608與光源612相連（如氙氣燈或20瓦的鹵素燈）。

接著，含有預定濃度試劑504的溶液（如某種免疫抗原）流過流動槽602，這樣，膜502上就吸附上一層抗原504。洗滌流動槽，使增加的抗原層504的厚度保持固定。這時用蛋白質阻斷反應。然後再洗滌一次。

最後，讓樣本溶液在一定時間內流過流動槽602。如果樣本溶液內含有與抗原504互補的抗體506，它們就會在槽內結合，這樣槽內膜的厚度就會增加。由於蛋白質分子

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通常小於光源612發射光波的波長，所增加的單分子蛋白質層可以被認爲只是增加了膜的厚度。

攝譜儀610用於測定不同時間內反射光波的光譜和强度。如圖4所示，當膜的厚度增加時，光譜攝製儀610第一次輸出爲A，第二次輸出爲B。膜厚的增量Δ可以由菲涅爾定理(Fresnel's law)確定。即，由薄膜反射的干涉光的光强I可以表示如下：

$$I = I_1 + I_2 + 2\sqrt{I_1 I_2}\cos\left(\frac{2\pi\Delta}{\lambda}\right)$$

其中，Δ即光程差(effective optical path difference)，λ爲入射光的波長。因I_1和I_2强度接近，可近似認爲兩者相等。

設$I_1 = I_2 = I_R$，上式可簡化爲：

$$I = 2I_R\left(1 + \cos\left(\frac{2\pi\Delta}{\lambda}\right)\right)$$

因此，有效光程差Δ（以及膜厚）可以由反射光的光强和光波的波長來確定。

雖然以上討論的微管Fabry-Perot干涉儀的優勢在於不需要標記，以及檢測結果不僅限於最終數據等。但是它仍然存在許多缺點。首先是微管尺寸仍然較大，從而需要較多量的檢測樣本，或要求樣本濃度高。其次該方法對於實現大量並行測試有一定困難。最後較大的尺寸使它不合適做體內檢測。

五、發明說明（　）

發明概要

根據上述現有技術中存在的問題或不足，生物感應器應從以下幾個方面進行改進：

（1）結構簡單，造價低，使用方便，小型探針式；

（2）可同時達到多種和並行化驗目的；

（3）不使用不穩定的或有毒的試劑或指示劑；

（4）可以進行體內化驗；

（5）能够連續採樣來監視反應過程，同時也能測試反應終值；

（6）允許即時數據分析；

（7）體內檢查時，爲了安全，要保證電隔離；

（8）能進行即時校正；

（9）較小的尺寸；

（10）　能防治非互補的吸附；

（11）　高靈敏度和大的線性範圍。

本發明的目的在於，提供一種改良式應用相位追蹤法的光纖生物檢測儀，該檢測儀採用了光纖生物感應器，克服了上述已知生物感應器的缺點。尤其是這種生物感應方法能通過光纖探針檢測樣本溶液中物質的濃度，其中至少一層是能吸附待測目標生物（或化學）分子的互補材料。當待測分子吸附到互補材料表面或其內部後，將改變反射干涉光的光譜分布。這種譜線偏移即用來定量或定性地分析樣本分子的濃度、附著速率、以及幾何尺寸的變化。

該光纖探針頂端塗有能够與待測物質發生生物化學反應的試劑。

五、發明說明（　）

爲了實現上述目的，本發明採用的技術方案是：該應用相位追踪法的光纖生物檢測儀，包括

a）光源804；

b）一個光纖生物探針700；

c）用來檢測由反射光束形成的干涉光光譜圖形的檢測器818、829；

d）一個用於耦合光源和光纖探針，以及耦合光纖探針和檢測器的耦合器

或連接器802；

e）一個用來確定檢測器818二次檢測到的干涉光光譜圖形的相位，並檢測由兩次圖形的相位移動所確定的待測物質的濃度的信號處理器；

信號處理器包括：微處理器830程序存儲器832、RAM834，並按常規的方法連接；

f）一個相位追踪器822；

g）一個輸出裝置824；

h）一個周期信號產生器820；

i）光學耦合器808、812；

j）光學波導806、828、816、814 、810；

其特徵在於：

所述光纖生物探針700是一根末端塗有試劑的光纖，包括一節光纖，其根部用於接收入射光束，其末端塗有一層或幾層材料和試劑，光纖生物探針至少要產生由入射光束所產生的反射光束，光纖生物探針700通過連接器802與光纖生物檢測儀的光學波導814相連；

五、發明說明（　）

所述光源804發出的光束，射入諸如光纖這樣的光學波導，通過一個光學耦合器808，用光學的方法連接一光學波導806與另一光學波導828，光學波導828連接檢測器829，檢測器829與周期信號產生器820相連；

光學耦合器812還將光學波導814與另一個光學波導816相聯，光學波導816與檢測器818相聯，檢測器818與周期信號產生器820相連；

光學耦合器808還將光學波導806與另一個光學波導810光學耦合，光學耦合器812將光學波導810和另一個光學波導814光學耦合；

光學波導814通過耦合器802與生物探針700相聯；

相位追踪器822與周期信號產生器820、輸出裝置824、信號處理器互連；周期信號產生器820也與信號處理器互連；光源804、檢測器818、輸出裝置824均與信號處理器互連。

本發明的其它特點在於：所述檢測器818、829是光譜儀(spectrometer)，還包括一個一維電荷耦合元件（CCD）；所述光學耦合器808是“Y”型耦合器；

所述光源804是寬帶光源或是可調的雷射二極體。

所述光學波導806、828、816、814 、810 是單模光纖(single-mode optical fiber)，也可以使用多模光纖(multi-mode optical fiber)，光纖直徑最少3μm，最好能達到100μm。

實施本發明的應用相位追踪法的光纖生物檢測儀的另外一種技術方案是，在上述技術方案中還包括

五、發明說明（　）

a）一個用來調節光源提供光束的頻率與光源相聯的頻率調節器1006；

b）一個用於檢測樣本溶液中第二種待測物質的第二個光纖探針；

c）一個光學合波多工器(optical multiplexer)1102，用於連接光源和每一根光纖探針，即用時分方式連接光源和光纖探針；

d）一個光學分波多工器(optical demultiplexer)1108，用於連接每一根光纖探針和檢測器；

光源804由頻率信號發生器1006驅動的雷射二極體1004；相位追踪器822與頻率信號發生器1006同步。

所述光學信號多路選擇器和光學信號分配器要求同步，保證在任一時刻都只有一根光纖探針和光源相聯。

所述光學波導806、828、816、814、810可以是單模光纖或多模光纖。

該光纖探針的製備包括以下步驟：（1）將光纖探針末端浸入樣本溶液；（2）在光纖根部加上光源；（3）至少檢測兩束光，第一束光是由光纖末端表面與試劑層的界面反射回來的，第二束光是由試劑層和樣本溶液的界面反射回來的；（4）第一次檢查兩束光形成的干涉圖形(interference pattern)；（5）第二次檢查兩束光形成的干涉圖形；（6）由干涉圖形是否發生移動來確定樣本溶液中是否含有待測物質。物質的濃度可以由干涉圖形的移動量和兩次檢查得到的條紋的不同來確定。

五、發明說明（　）

爲了得到最佳結果，檢測的每一步都應該包括以下步驟：（1）將兩束光形成的干涉光束送入光譜儀；（2）根據光譜圖的分布確定一個周期函數；（3）確定周期函數的相位。

該檢測儀還有另一種實施例，光纖探針根部光源的頻率是可調的，檢查樣本溶液中是否含有待測物質的步驟與光源頻率變化同步進行。

該檢測儀使用探針一次性檢測樣本溶液中所含待測物質的濃度。該探針包括一根有完整頭尾的光纖，光纖末端塗有試劑層。試劑層與待測物質發生反應。光纖部分有一定的折射率。只要待測物質附著到試劑層上，就得到由試劑層與待測物質組成的新薄膜層。新層可以認爲具有相同的折射率。光纖部分可以是單模或多模光纖，直徑最少爲3微米，最好能達到100微米。

光纖末端所塗試劑可以是抗體、抗原、合成物質或天然蛋白質、RNA、DNA片段或化學試劑。

本發明可以用來檢測樣本溶液中物質的濃度。該檢測儀包括一個提供光束的光源、光纖探針檢測器、光纖耦合器、光纖連接器和信號處理器。

光纖耦合的第一條光纖，其根部用來接受入射光，耦合器的第二條光纖的根部用於將反射過來的干涉光束傳遞給檢測器，第三條光纖的底端用於連接光纖探針。光纖探針的根部連接到光纖耦合器上，末端塗有一層處理過的試劑。光纖探針至少可以由入射光產生第一束反射光和第二束反射光。探測器用來檢測兩束反射光相干後產生的干涉

五、發明說明（　）

圖案。光纖耦合器將光源發出的光傳輸給光纖探針，將光纖探針與檢測器相聯。信號處理器既可以用來確定兩次干涉圖形的相位、又可以根據兩次干涉圖形相位的不同確定待測物質的濃度。

爲了更好地實施該系統，檢測儀要選擇光譜儀，由分光器和一維CCD元件（如1*1024 CCD）組合而成。

爲更好地實施該檢測儀，信號處理器要包括一個周期信號產生器、一個相位追踪器和一台個人電腦。周期信號產生器用於產生兩個周期信號，第一個周期信號由檢測器第一次檢測到的干涉圖形得到，第二個周期信號由檢測器第二次檢測到的干涉圖形得到。相位跟追器用於確定第一個周期信號和第二個周期信號的相位，計算機用來確定相位差，並由相位差計算出樣本溶液中待測物質的濃度。

爲更好地實施本發明，耦合器爲“Y”型耦合器，光源爲寬帶光源或高級發光二極體。

該檢測儀還有另外一種實施例，檢測儀包括一個與光源相聯的頻率調節器，用來調節光源所提供光束的頻率。這時，信號處理器要與頻率調節器同步。

還有一種形式，該檢測儀包括另一個光纖探針，一個光學合波多工器和一個光學分波多工器。第二個光纖探針用來確定樣本溶液中第二種待測物質的濃度。光學多路選擇器用來連接光源和兩個光纖探針，用時分方式將光源和兩個光纖探針相聯。多路光學數據分配器用來連接兩個光纖探針和檢測器。合波多工器和分波多工器要同步。

五、發明說明（　）

圖示簡單說明

圖1a、1b、1c和1d顯示傳統的夾層型、位移型、競爭型光纖螢光生物感應器。

圖2a是傳統的表面等離子體感應器的截面示意圖。圖2b是表面等離子體感應器中入射光的入射角與反射光强之間的關係曲線。圖2c是光纖表面等離子體感應器探針的切面圖。圖2d是利用光纖表面等離子體反應生物探針的系統方塊圖。圖2a到2d所示爲傳統的裝置。

圖3是一種傳統的輸出光柵生物探針的工作過程圖示。

圖4是傳統的微管反射干涉儀。生物感應器在第一時間t1和第二時間t2的反射波長與光强的關係曲線。

圖5所示是傳統的微管生物感應器中所用的流動槽的切面示意圖。

圖6所示是傳統的微槽生物感應器方法的系統實施圖。

圖7a和7b所示是本發明的生物感應器所用的生物探針的工作過程。

圖8所示是本發明的生物感應器的第一種實施例。

圖9a和9b所示是此生物感應器所用光譜儀接受到的移動的光譜分布圖。

圖10所示是此生物感應器的第二種實施例。

圖11所示是此生物感應器用的合波多工器方式。

五、發明說明（　）

圖示主要元件符號說明

100 光纖

102 試劑（抗原）

104 溶劑

106 互補抗體

108 溶液

110 試劑（抗原）

112 標誌

120 試劑（抗原）

122 試劑（抗體）

124 酶標記

130 薄膜

140 與 120 互補之抗體

150 樣本溶液

202 棱鏡

204 金屬層

206 入射光

208 絕緣體

210 光纖芯線

212 光纖外殼

214 金屬

216 樣本溶液

218 銀鏡

222 分光器

五、發明說明（　）

224 連接器

226 模式編碼器

304 平面波導

306 高折射率膜

308 玻璃基質

310 光柵

312 容器

314 液體樣本

316 透鏡

318 一元位置敏感像檢測器

320 類比數位轉換器

322 個人電腦

500 以玻璃片為基底的干涉器

502 聚苯乙烯膜

504 試劑（抗原）

506 互補抗體

508 入射光

510 反射干涉光強

512 反射干涉光強

514 基底

602 流動槽

604 光纖

606 分支

608 分支

五、發明說明（　）

610 光譜儀

612 光源

614 個人電腦

700 光纖探針

702 光纖

704 試劑（抗原）

706 交界面

708 試劑暴露的外表面

710 入射光

712 反射光

714 入射光之一部份

716 第二束反射光

718 入射光之又一部份

720 入射光之一部份

722 入射光之另一部份

724 第二束反射光

726 724 反射光之一部分

728 抗體外表面

730 抗原與抗體層交界面

732 抗體層

734 樣本溶液

736 互補抗體

738 非互補抗體

760 716 反射光之一部份

五、發明說明（　）

780 試管

800 生物感應器光學分析儀

802 連接器

802' 連接器

804 光源

806 光學波導

806' 光學波導

808 光學耦合器

808' 光學耦合器

810 光學波導

810' 光學波導

812 光學耦合器

812' 光學耦合器

814 光學波導

814' 光學波導

816 光學波導

816' 光學波導

818 光譜儀

818' 光譜儀

820 周期信號產生器

820' 周期信號產生器

822 相位追蹤器

822' 相位追蹤器

824 輸出裝置

五、發明說明（　）

824'輸出裝置

826 電腦/網路

826'電腦/網路

828 光學波導

828'光學波導

829 可選擇的光譜儀

829'可選擇的光譜儀

830 微處理器/ASIC

830'微處理器/ASIC

832 程序存儲器

832'程序存儲器

834 RAM

834'RAM

836 命令和數據通道

836' 命令和數據通道

1000 生物感應器光學分析儀

1004 激光二極體

1006 頻率信號發生器

1102 光學合波多工器

1104 計數器

1106a 探針 1

1106b 探針 2

1106c 探針 n

1108 光學分波多工器

五、發明說明（　）

1110a 光學輸入/輸出耦合器

1110b　光學輸入/輸出耦合器

1110c　光學輸入/輸出耦合器

S1 試劑厚度

S2 抗原+抗體層總厚度度

發明詳述

下面結合附圖7a、7b、8、9a、9b、10及11對本發明作進一步的詳細描述。

圖 7a 和 7b 所示的是本發明原理圖。如圖 7a 所示，生物感應器探針 700 包括一根光纖 702 和塗在光纖 702 末端的試劑 704。試劑 704 可能是某種抗原，如免疫抗原。也可能是一種特殊的抗體、化學物質、DNA 片段、酶或蛋白質。將一定濃度的試劑 704 在一定時間內塗到光纖 702 的末端，確定光纖 702 的末端的確形成了一層試劑 704，然後將該裝置清洗和包裝。有經驗的人還可以用其他方法在光纖 702 的末端塗上試劑 704。可根據不同的試劑決定不同的塗敷方法。入射光束 710 從光纖根部傳到光纖末端。在試劑層 704 和光纖 702 的交界面將會有第一束反射光 712 被反射回去，同時，入射光束 710 的一部分 714 會繼續通過試劑 704。在試劑 704 的暴露的外表面 708 上，第二束反射光 716 被反射回去，而入射光束 710 的又一部分 718 將繼續射向與試劑層 704 相鄰的媒介。由入射光束 710 的一部分 714 所反射的反射光 716 的一部分 760 將通過光纖 702 傳到根

五、發明說明（　）

部，反射光716的另一部分將在交界面706處反射回試劑層704（未畫出）。

下面將詳細討論，在光纖702的根部，反射光712和760得到檢測和分析。沿著光纖702的任一給定點，包括它的根部，反射光712和760會有一個相位差。根據這個相位差，可以檢測出試劑層704的厚度。

如圖7b所示，將探針700浸入樣本溶液734，檢測與抗原704互補的抗體736是否存在，以及樣本溶液734中抗體736的濃度。由於抗體736與抗原704的特性決定了它們之間會發生特別的反應，抗體736會粘附在試劑層704上，從而在一定時間內，在試劑層704上形成一個抗體層732。然而，非互補的抗體738就不會粘附在試劑層704上。對樣本溶液734來說必須減少探針700與（除抗體外）其他物質發生粘和的可能性。也就是說，要使探針700上的試劑704減少與非互補抗體738之間發生粘附的可能性。

例如，一個有代表性的例子是，要被檢測的分子（如抗原和抗體）的尺寸應該遠小於入射光710的波長。因此，從光學的角度來看，試劑層704和抗體層732可以看做一個單層。也就是說，從光學角度講，圖7b所示的試劑層704和抗體層732的交界面730通常並不明顯。這樣，圖7b所示的試劑層704和抗體層732的組合層同圖7a中試劑層704具有相似性。不過，兩層的總厚度S2比單獨試劑層704的厚度大。因此，與圖7a中的探針700相似，當入射光710進入光纖702的末端時，在光纖702和組合層的界面706上，入射光710的一部分712被反射回去，同時，入射光

五、發明說明（　）

710的另一部分720繼續通過組合層和樣本溶液734。720的一部分724 被反射回去，而720的另一部分722繼續通過樣本溶液734。對反射光724來說，它的一部分726返回到光纖702中，而另一部分（未畫出）被界面706反射到組合層中。

沿著光纖702的任一給定點，包括它的根部，反射回來的光束712和726會呈現出一個相位差。根據這個相位差，組合層的厚度S2可以檢測出來。

通過比較組合層的厚度S2和試劑層704的厚度S1，就可以確定抗體層732的厚度。根據這個厚度，互補抗體736在樣本溶液734中是否存在就可以確定。更進一步，組合層的厚度S2可以在離散時間點上抽樣。用這種方法，組合層的厚度S2和試劑層704的厚度S1之間的厚度差增加的速率（例如，抗體層732的厚度增加速率）就可以測出。根據這個速率，在很短的一段培養期內就可以測出互補抗體736在樣本溶液734中的濃度。

圖8描述的是進一步改進的應用上述生物探針700的生物感應器的第一種實施方法。再重復一遍，包括光纖702以及塗在光纖702末端的試劑層704在內的生物探針700，要浸入樣本溶液734中，從圖中被放大的部分可以看出，光纖外殼包裹著光纖芯直到光纖芯的末端。更特別的是，光纖外殼從頭到尾包裹著光纖芯，樣本溶液盛在試管780裏，光纖探針700通過連接器802與生物感應器光學分析儀800相聯。

五、發明說明（　）

生物感應器光學分析儀800包括光源804、光譜儀818、周期信號產生器820，相位追踪器822、以及輸出裝置824。生物感應器光學分析儀800可以用許多方法實施。例如，（1）通過外部電腦或電腦網路826的命令；（2）通過微處理器830的命令，該微處理器執行程序存儲器832發出的指令，這套裝置還包括RAM834；（3）或通過專用特殊應用積體電路（Application Specific Integrated Circuit, ASIC）830發出的命令。

在第一種實施例中，光源804是寬頻光源，如發光二極體。光源804也可以是鎢鹵素燈。光源804發出的光束，射入諸如光纖這樣的光學波導，也可以加一個光學耦合器808，用光學的方法連接光學波導806與另一光學波導828，光學波導828連接一個可選擇的光譜儀829。光譜儀829最好包括一個一維電荷耦合器件（CCD），如1*1024 CCD，並與一個周期信號發生器820相連接。可選的光譜儀829可以是600到700nm的光譜儀。

光學耦合器808還將光學波導806與另一個光學波導810光學耦合。光學耦合器812將光學波導810和另一個光學波導814光學耦合。光學波導814通過耦合器802與生物探針700相聯。

光學耦合器812還將光學波導814與另一個光學波導816相聯。光學波導816與光譜儀818相聯。同光譜儀829一樣，光譜儀818最好包括一個一維CCD，如1*1024 CCD，並與周期信號發生器相聯。

五、發明說明（　）

光源804發出的光，通過光學波導806、光學耦合器808、光學波導810、光學耦合器812、光學波導814和光學耦合器802被生物探針700接收到。從上面對圖7b的討論中知道，兩束反射回來的光束712和726通過生物探針後返回，並通過耦合器802、光學波導814和光學波導816後被光譜儀818接收到。如上所述，由於組合層具有厚度S2，反射光束712和726會有微弱的異相現象(out-of-phase)。因此，根據菲涅爾理論，反射光束712和726會在光譜儀818上形成繞射圖形(diffraction pattern)。隨著組合層厚度S2的增加，繞射圖形會發生移動。

當光譜儀818記錄下CCD的像素之後，周期信號發生器820就會產生一個周期信號波形。由繞射圖決定的周期信號波形（如正弦波）的相位能被相位追踪器822檢測出來。通過比較正弦波的相位，該相位在不同時間光譜儀採樣得到的繞射圖決定，組合層厚度S2的增加的速率就可以檢測出來。得到相位數據之後或同時，可以確定S2增加的速率。

回到圖7a，在生物探針700被浸入樣本溶液734之前，由試劑層704的厚度S1，也可以得到反射光束712和760形成的一個繞射圖形。圖9所示爲光譜儀820上一維CCD器件所顯示的繞射圖形的一部分（即在生物探針被浸入樣本溶液734之前）。圖9b所示爲光譜儀820上一維CCD器件所顯示的繞射圖形的一部分。比較圖9a和圖9b所示圖形，會發現繞射圖形發生了移動。根據移動量，可以確定

五、發明說明（　）

樣本溶液734中與抗原704互補的抗體736是否存在。生物探針700浸入樣本溶液734之後，通過不同時間光譜儀對一維CCD的取樣結果，可以測出圖形移動變化的速率，並由此確定在樣本溶液734中互補抗體736的濃度。

在如圖8所示的第一種實施例裏，光學波導806、810、814、816和828最好是單模光纖，如通信級單模光纖。不過也可以使用多模光纖。比如梯度光纖。光纖直徑最少3μm，最好能達到100μm。

光學耦合器808和812最好是“Y”型光纖，也可以是“X”型光學耦合器。不過，若使用第二種光學耦合器，就要提供膠化匹配指數(index matching gel)，用於去掉開放末端的反射雜訊。

與光源804耦合的光譜儀829，只在光源804的雷射二極體的光譜不穩定時才需要。特殊情況是，要區別由生物探針700的末端厚度變化導致的相移與光源頻率移動帶來的相移時，要用到光譜儀829。然而，如果光源804的雷射二極體的光譜非常穩定，光源804以及光學耦合器808和光學波導828就不再需要了。

圖10是此生物感應器的第二種實施例。包括一個可增補的生物感應器光學分析儀1000。系統的組成基本類似於圖8所示的系統，除了：（1）寬帶光源804由頻率信號發生器1006驅動的雷射二極體；（2）相位追踪器822必須與頻率信號發生器1006同步。頻率信號發生器1006生產一個斜坡頻率(ramped frequency)驅動信號（或“線性調頻脈衝”,chirp）。該系統的工作過程與圖8所示系統工

五、發明說明（　）

作類似。不過，相位追踪器822必須與頻率信號發生器1006同步。另外，光學波導806'、810'、814'、816'和828'也必須要用多模光纖。

由於生物探針700相對較小並允許移動，所以可以即時檢測，也可以用多個生物探針而不是一個來檢查同一溶液中的不同物質。如圖11所示，一個光學合波多工器1102在某輸入端接收的從光源（未畫出）射出的一束光（如混合頻率光束）。通過一個輸入控制信號，光學合波多工器1102將輸入信號通過一個單刀多擲開關與輸出信號相聯。輸入控制信號可以由時鐘計數器1104提供。光學合波多工器1102通過一個波導和連接器1110將一路或多路輸出信號與一個或多個生物探針相聯。一個或多個生物探針1106中的每一根都通過連接器1110與其對應的光學分波多工器1108的輸入端相聯。連接器1110可以類似上述的"Y"型連接器。根據輸入控制信號的內容，光學多路分配器1108將其N個輸入中的某一個輸出至光譜儀（未畫出）。雖然該例只給出了一個分時多路選擇器裝置，但分頻多路選擇器顯然也是可行的。

同理，當附著在光纖測試端的生物分子體積發生變化時，通過檢測反射干涉所產生的光譜分布圖的相位，可以推算體積變化的速率和大小。

綜上所述，改進的生物感應器具有簡單的結構，因此成本低，還可以製成一次性使用的產品。由於它體積小，可以同時做多種檢驗，從而使體內直接檢驗變得可行。另外，該生物感應器在工作中穩定可靠，沒有有毒的標記或

五、發明說明（　）

指示劑。還有，該生物感應器系統允許系統連續采集數據、末點數據采集和實時數據分析。由於數據測量是通過光信號進行通信的，該生物感應器系統要保證與病人電絕緣，這樣才可以進行體內直接檢驗。由於該生物感應器系統所用的生物探針相對樣本溶液來說是微不足道的（即可以忽略），所以，其他（非互補的）粘附可以達到最小的程度。由於該生物感應器方法應用了菲尼爾反射定律，因此它不僅高度敏感，而且還具有很大的線性度。

六、申請專利範圍

1、一種應用相位追踪法的光纖生物檢測儀，其係包括有：

a）一光源；

b）一第一光纖探針；

c）一第一及一第二檢測器，其係用於檢測由反射光束形成的干涉光光譜圖形；

d）一個連接器；

e）一信號處理器，其係用於確定該第一檢測器進行二次檢測到的干涉光光譜圖形的相位，並檢測由兩次圖形的相位移動所確定的待測物質的濃度；該信號處理器係包括有微處理器、程序存儲器以及RAM；

f）一個相位追踪器；

g）一個輸出裝置；

h）一個周期信號產生器；

i）一第一及一第二光學耦合器；

j）一第一光學波導、一第二光學波導、一第三光學波導、一第四光學波導以及一第五光學波導；

其特徵係在於，

該第一光纖探針係為是一根末端塗有試劑的光纖，包括一節光纖，其根部係用於接收入射光束，其末端塗有一層或幾層材料和試劑，該第一光纖探針至少要產生由入射光束所產生的反射光束，該第一光纖探針係經由該連接器而與該光纖生物檢測儀之該第四光學波導相連；

該光源所發出的光束係射入至該第一光學波導中，並經由以光學方式將該第一光學波導耦合至該第二光學波導的該第一光學耦合器而進入該第二光學波導，該第二光

六、申請專利範圍

學波導係與該第二檢測器相連，而該第二檢測器係與該周期信號產生器相連；

該第二光學耦合器還將該第四光學波導與該第三光學波導相連，該第四光學波導係與該第一檢測器相連，該第一檢測器係與該周期信號產生器相連；

該第一光學耦合器還將該第一光學波導與該第五光學波導以光學方式相耦合，該第二光學耦合器係將該第五光學波導和該第四光學波導以光學方式相耦合；

該相位追踪器係與該周期信號產生器、該輸出裝置、以及該信號處理器互連；該周期信號產生器亦與該信號處理器互連；該光源、該檢測器、該輸出裝置均與該信號處理器互連。

2、根據申請專利範圍第1項所述的光纖生物檢測儀，其特徵係在於，該第一及該第二檢測器係為光譜儀，其更包括有一個一維電荷耦合器件（CCD）；該第一光學耦合器係為Y型耦合器。

3、根據申請專利範圍第1項所述的光纖生物檢測儀，其特徵係在於，該光源係為寬帶光源或是可調的雷射二極體。

4、根據申請專利範圍第1項所述的光纖生物檢測儀，其特徵係在於，該第一、第二、第三、第四、以及第五光學波導係為單模光纖或多模光纖，其光纖直徑係最小為3 μm。

5、根據申請專利範圍第1項所述的光纖生物檢測儀，其特徵係在於：該光纖生物檢測儀更包括有：

一個用來調節該光源所提供光束之頻率而與該光源相連

（請先閱讀背面之注意事項再填寫本頁）

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六、申請專利範圍

的頻率調節器；

一個用於檢測樣本溶液中第二種待測物質的第二光纖探針；

一個光學信號合波多工器，其係用於連接該光源和該第一及第二光纖探針，即用時分方式連接該光源與該第一及第二光纖探針；

一個光學分波多工器，其係用於連接該第一及第二光纖探針與該第一及該第二檢測器；

該光源由頻率信號發生器所驅動的雷射二極體；該相位追踪器係與該頻率信號發生器同步。

6．根據申請專利範圍第5項所述的光纖生物檢測儀，其特徵係在於，該光學信號合波多工器和該光學分波多工器係為同步者，用以確保在任一時刻僅有該第一及該第二光纖探針中的一個會與該光源相連。

7．根據申請專利範圍第5項所述的光纖生物檢測儀，其特徵係在於，該第一、第二、第三、第四、以及第五光學波導係為單模光纖或多模光纖。

圖式

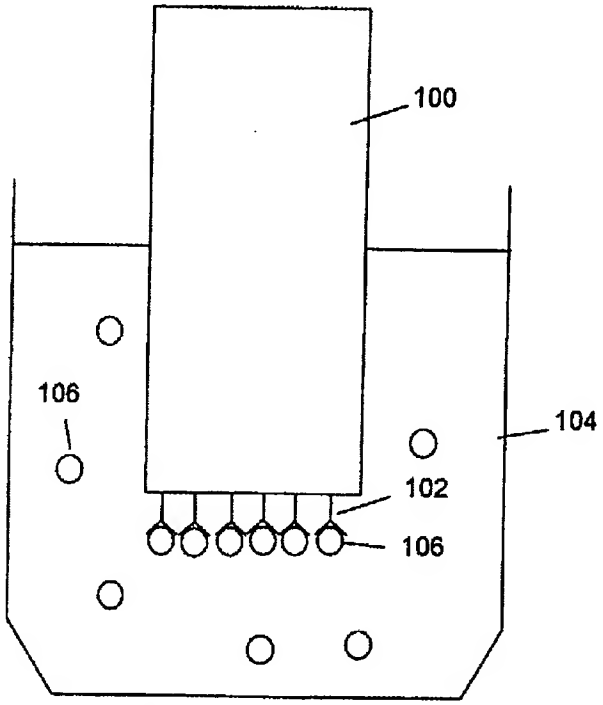

圖 1a（習知技術）

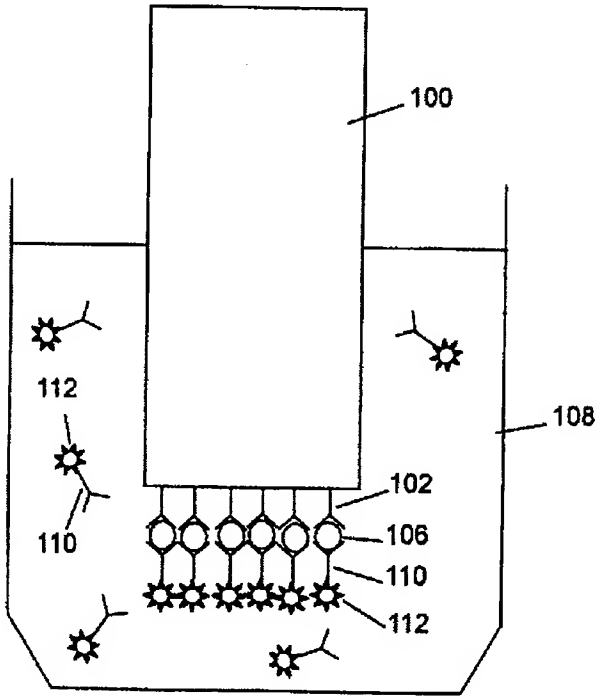

圖 1b（習知技術）

圖式

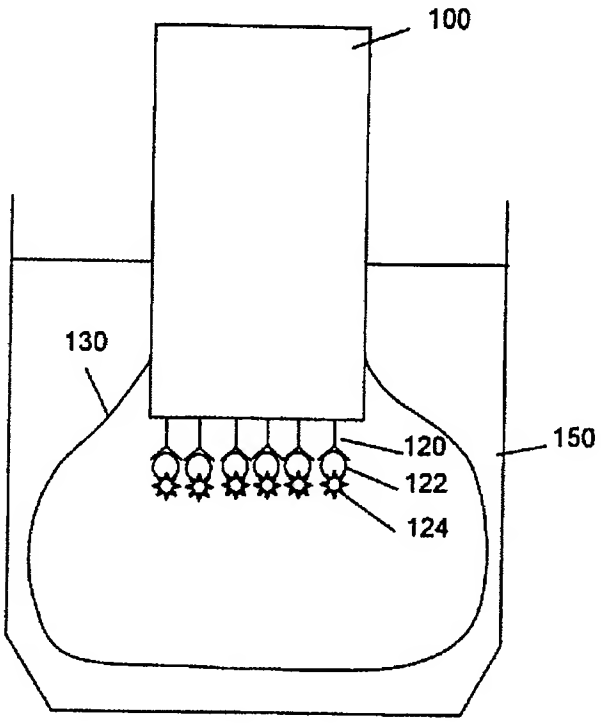

圖 1c（習知技術）

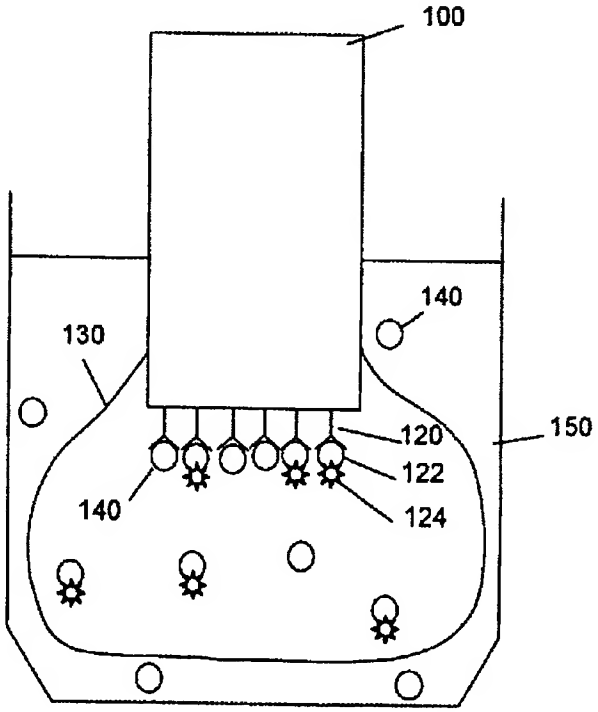

圖 1d（習知技術）

圖式

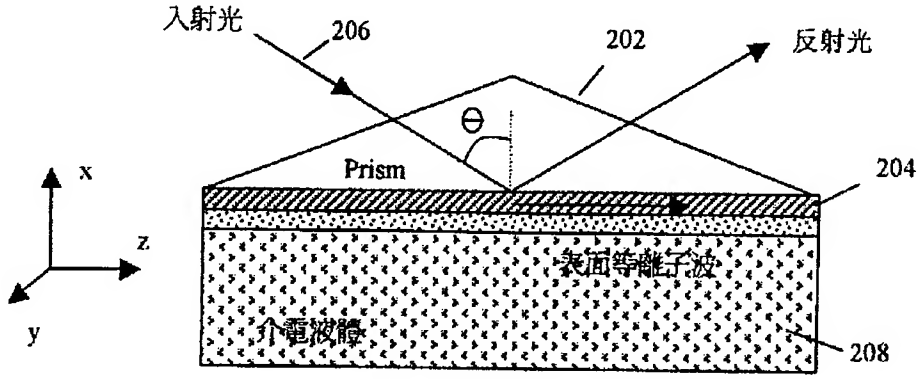

圖 2a（習知技術）

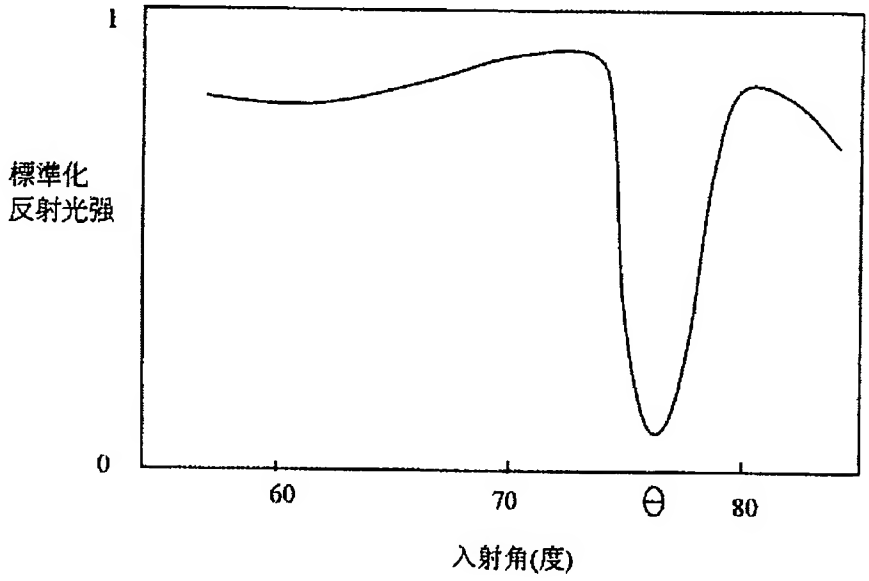

圖 2b（習知技術）

圖式

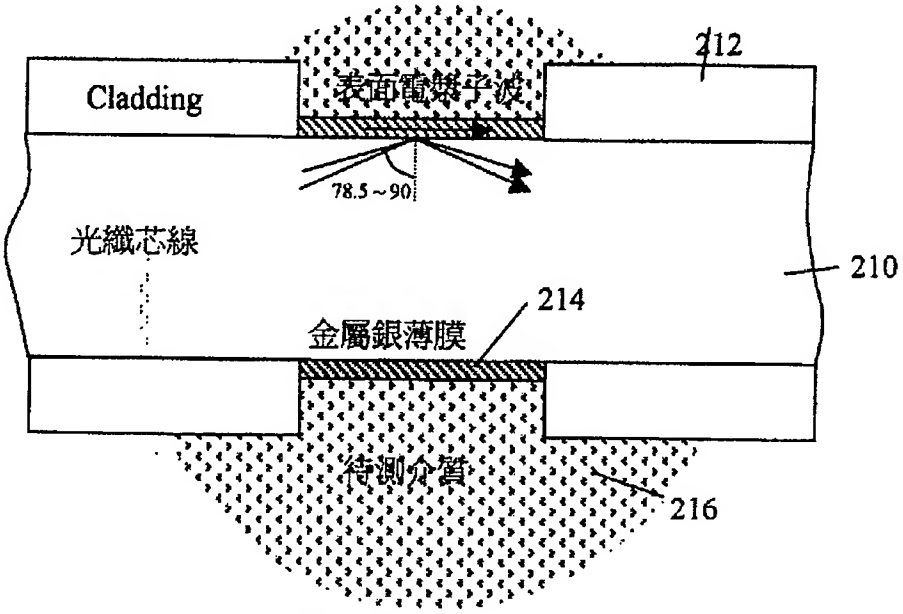

圖 2c（習知技術）

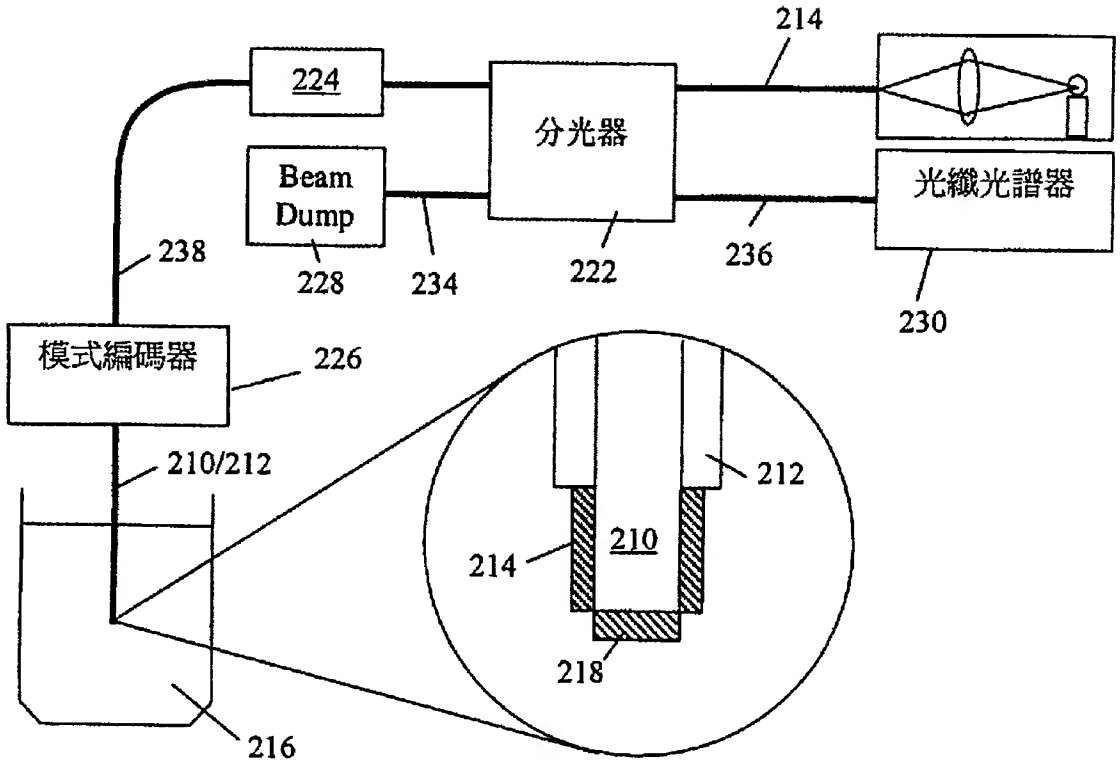

圖 2d（習知技術）

（請先閱讀背面之注意事項再行繪製）

裝 訂 線

圖式

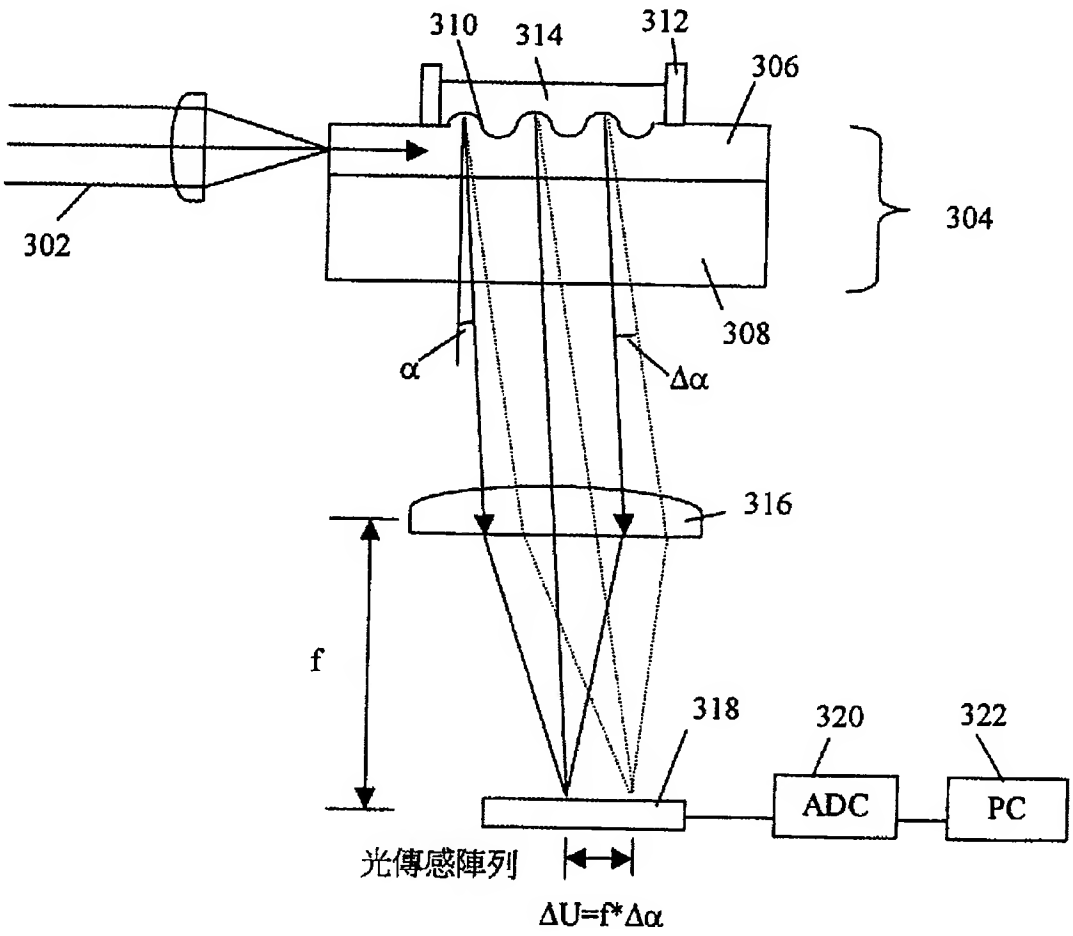

圖 3（習知技術）

圖式

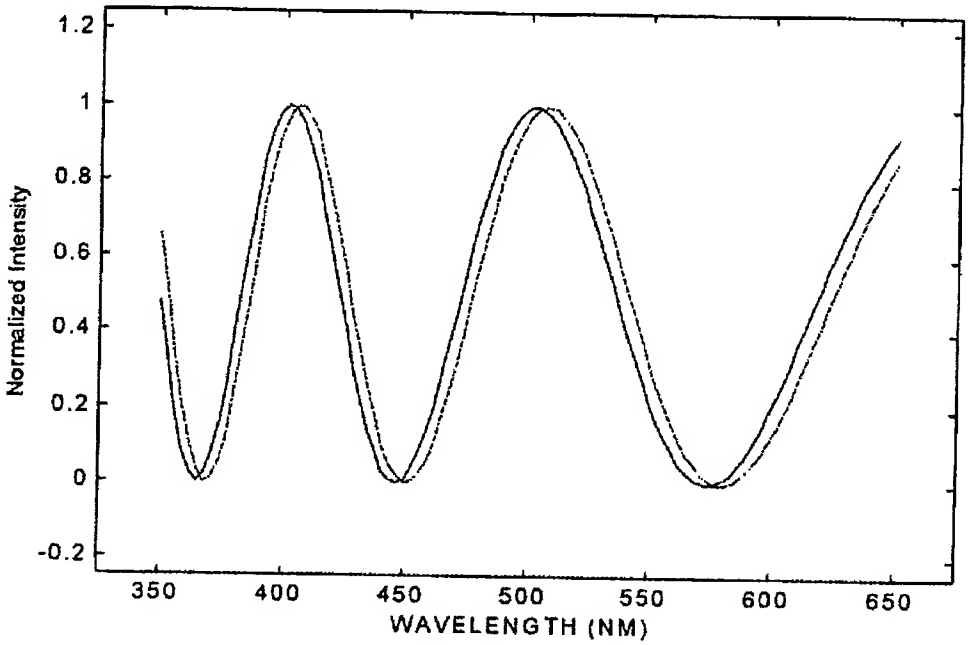

圖 4（習知技術）

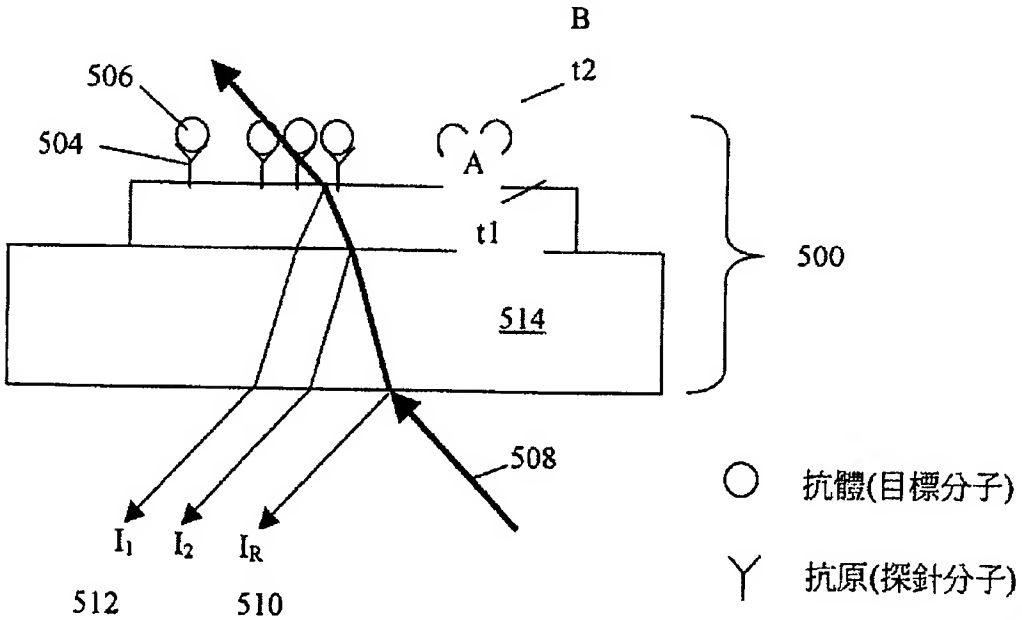

圖 5（習知技術）

（請先閱讀背面之注意事項再行繪製）

裝

訂

線

圖式

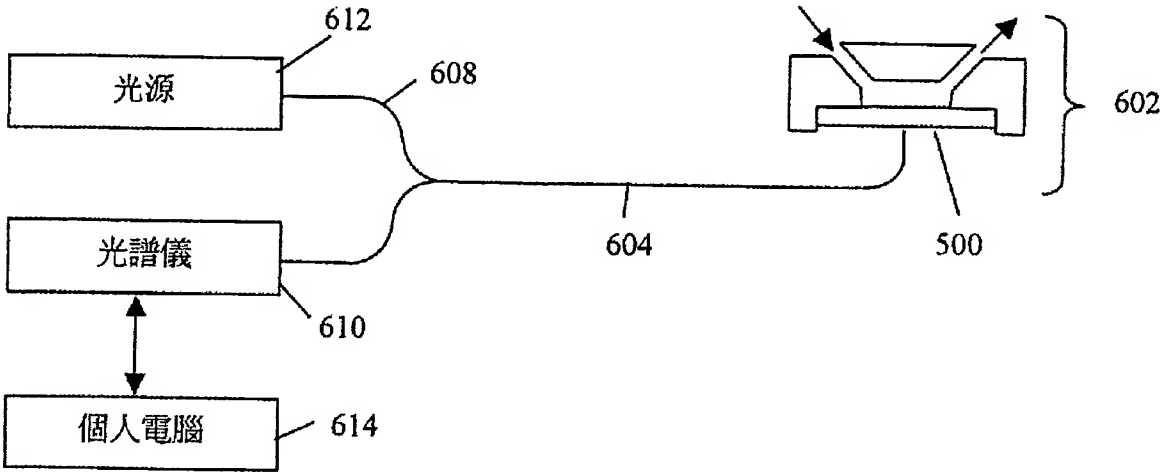

圖 6（習知技術）

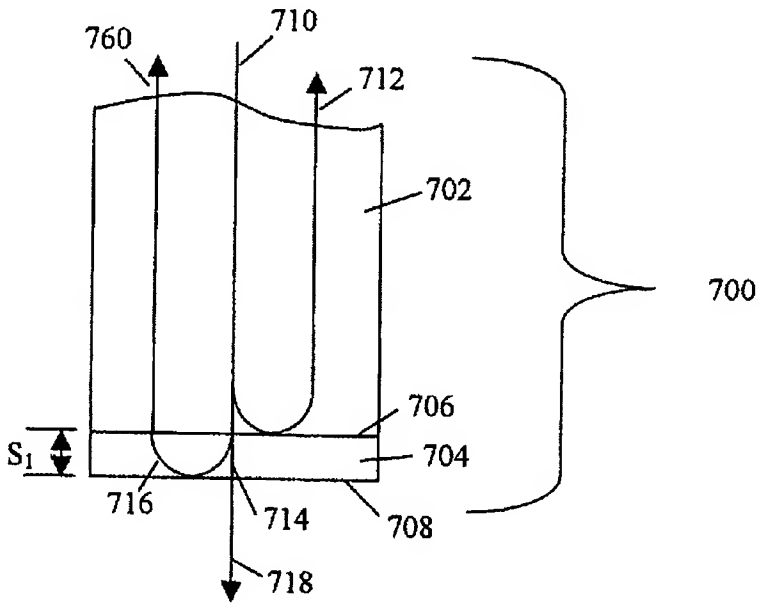

圖 7a

圖式

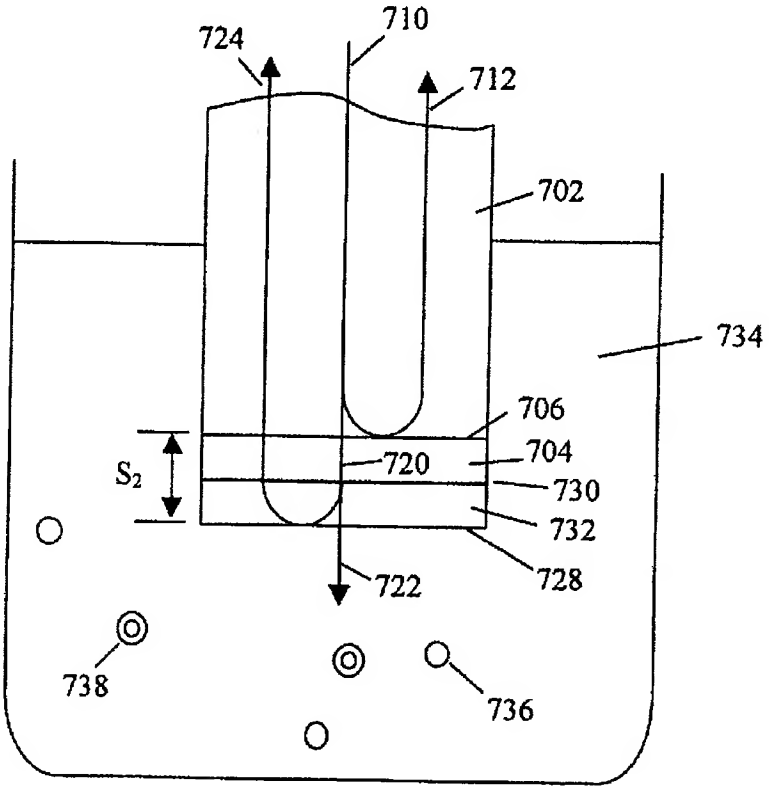

圖 7b

圖式

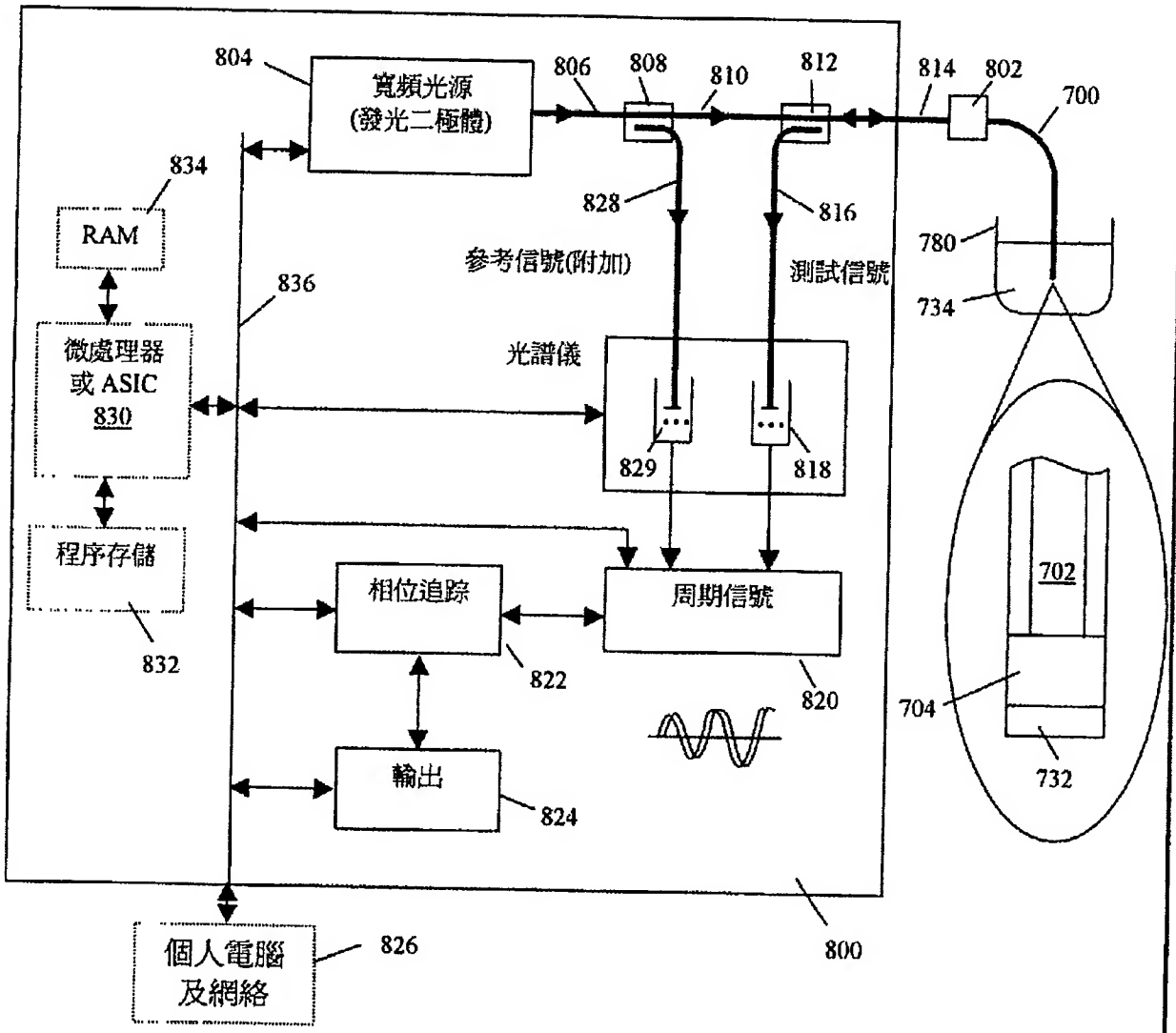

圖 8

圖式

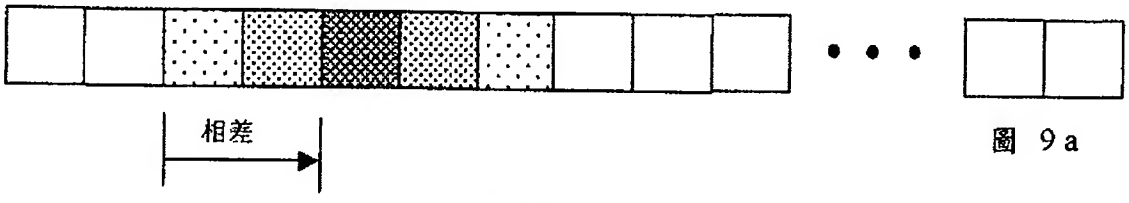

圖 9a

圖 9b

C9
D9

圖式

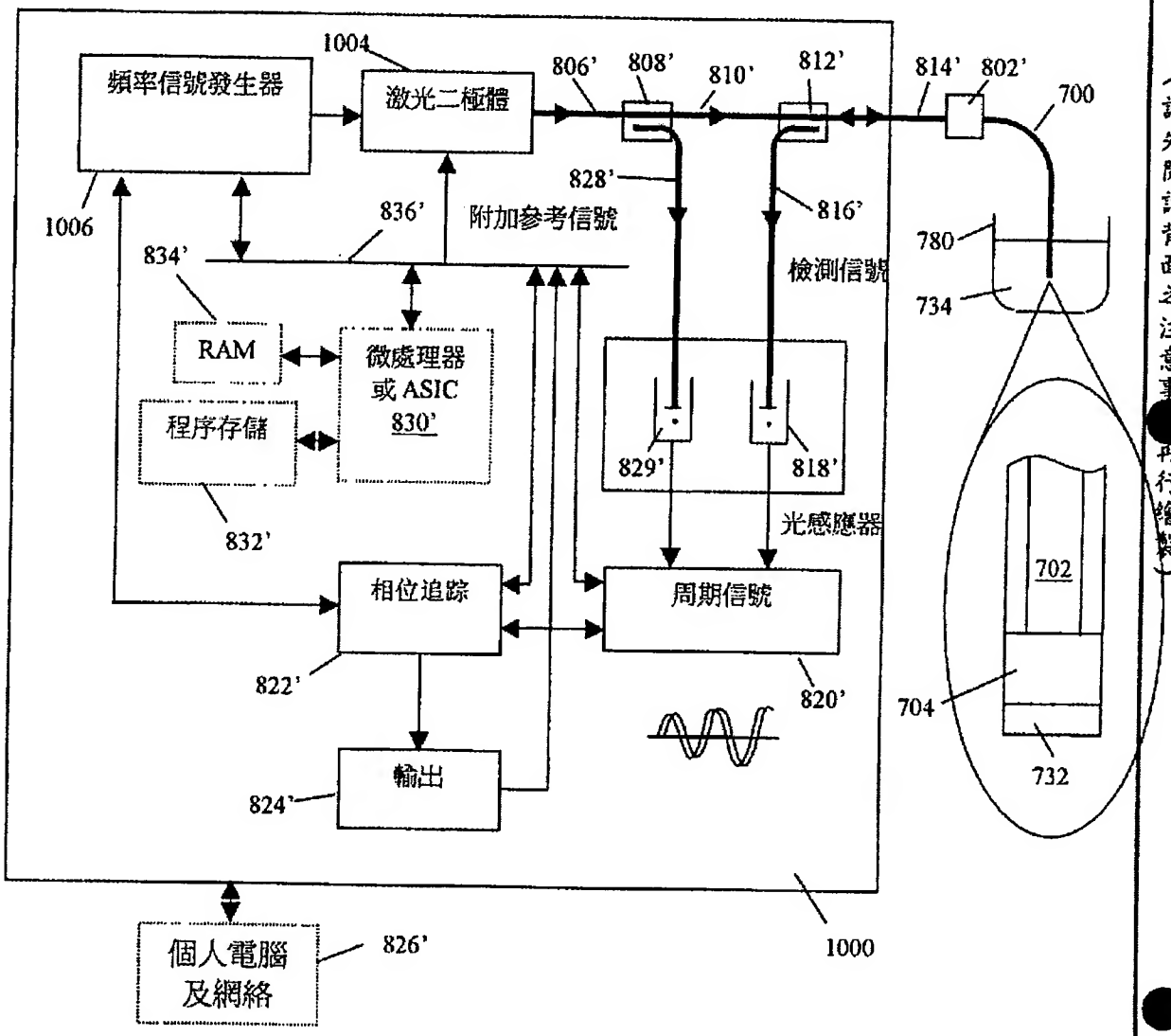

圖 10

（請先閱讀背面之注意事項再行繪製）

裝

訂

線

C9
D9

圖式

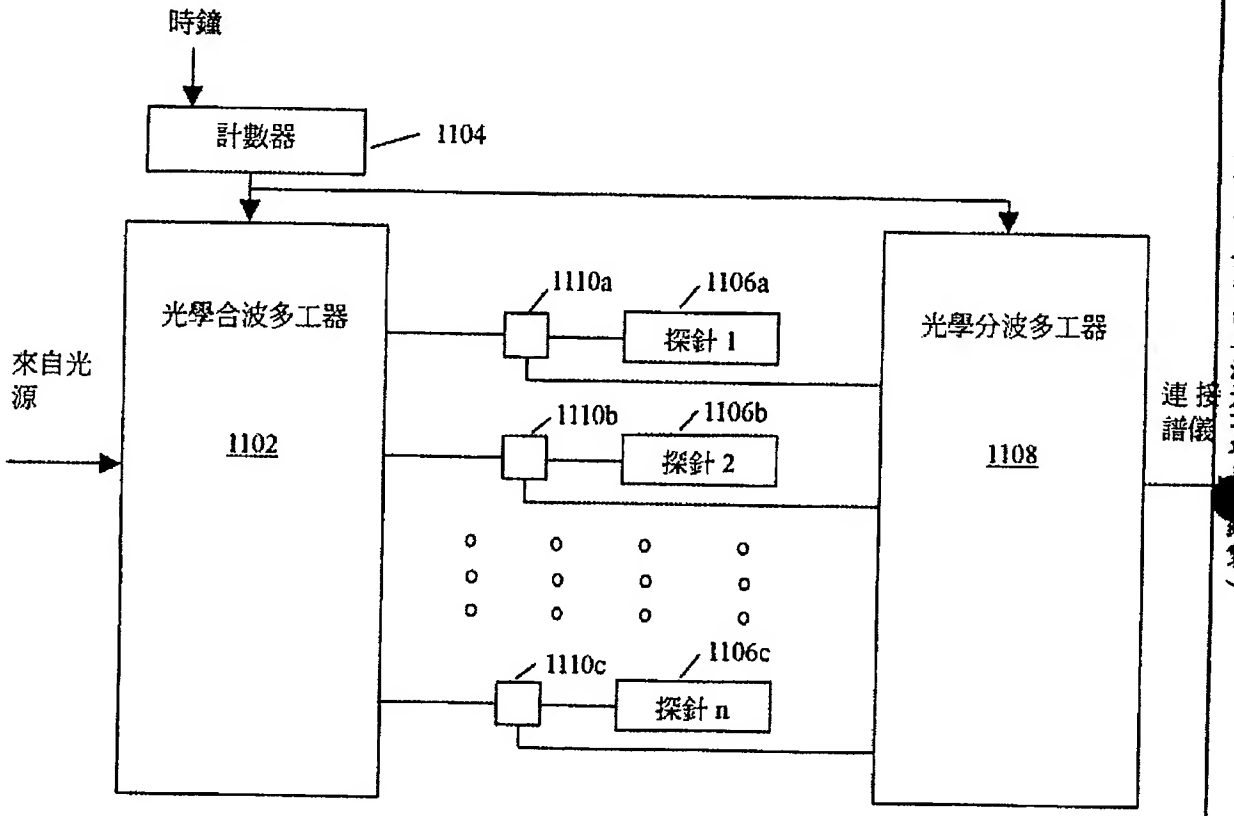

圖 11

（請先閱讀背面之注意事項再填寫）

裝

訂

線